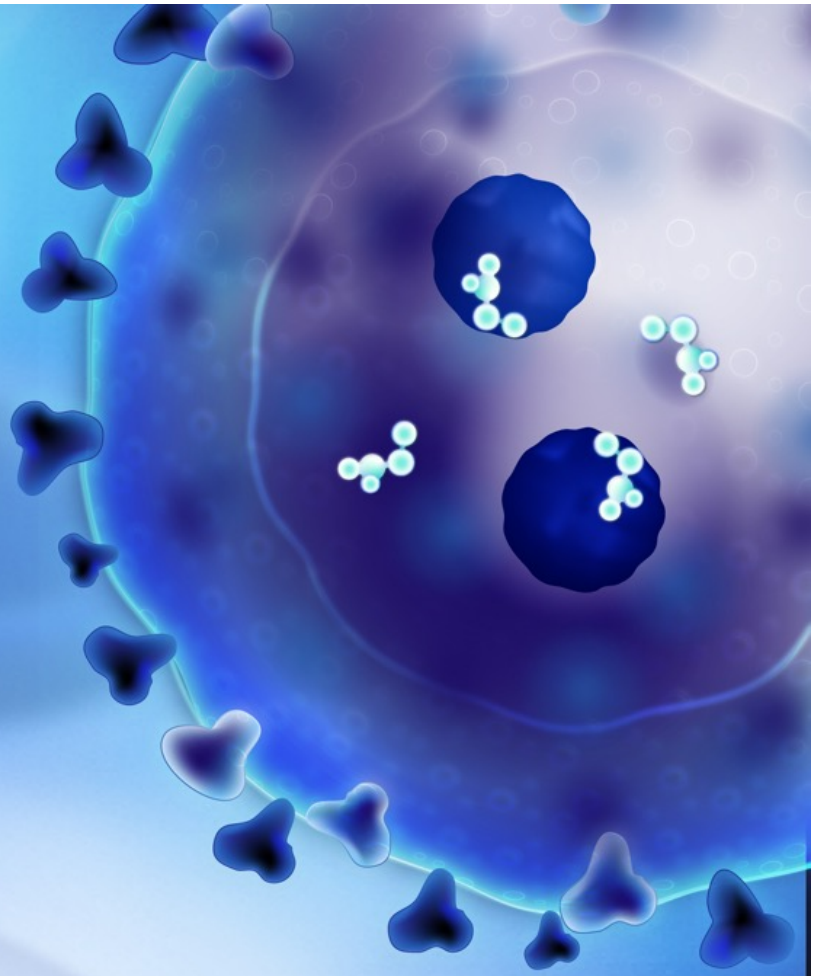
Menarini Stemline lecture at the
6th European Myeloma Network Meeting

Optimising the sequence of novel therapies from early relapse to improve the survival of patients with relapsed/refractory multiple myeloma

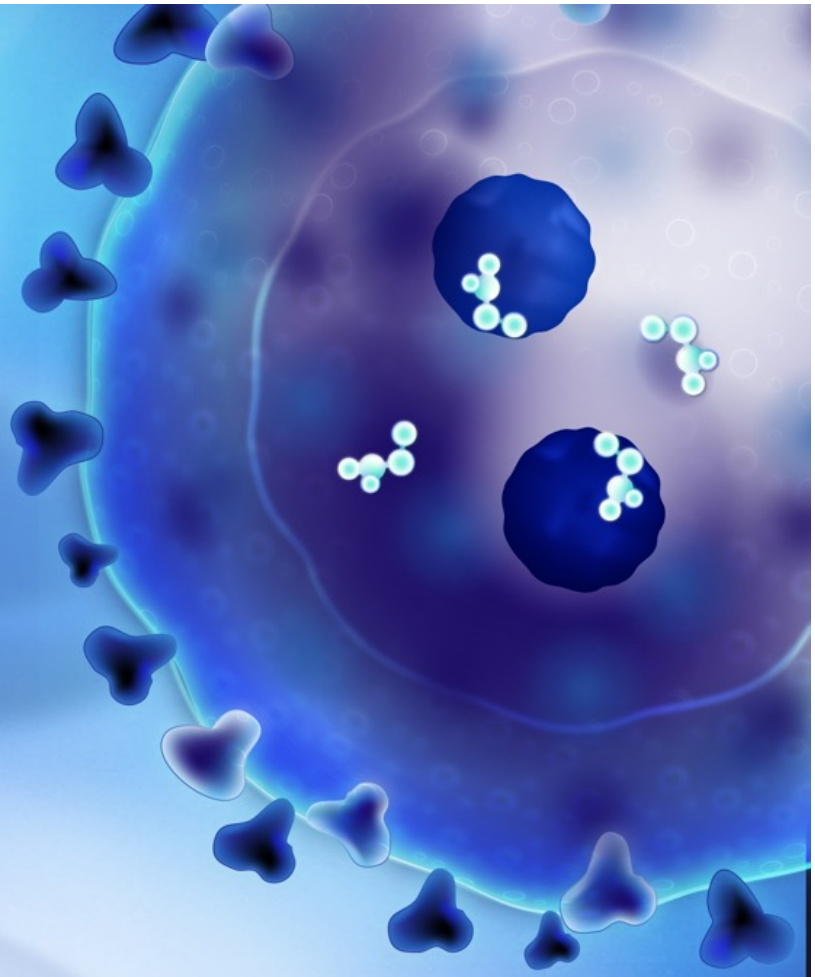
Friday, 11th April | 16:45–17:15
Divani Caravel Hotel, Athens, Greece
(in-person and live streamed)



MENARINI group
Stemline
A Menarini Group Company

Introduction

Evangelos Terpos
University of Athens,
Athens, Greece



MENARINI group
Stemline
A Menarini Group Company

Objectives

- Evaluate the key areas of unmet medical needs for patients with early relapsed multiple myeloma
- Summarise the impact of novel agents in the early relapsed multiple myeloma treatment paradigm and latest treatment guidelines
- Provide guidance on the combination and sequencing of novel therapeutic agents
- Highlight the optimal use of selinexor in the evolving multiple myeloma treatment environment

Faculty

Evangelos Terpos (Chair)

University of Athens, Athens, Greece

Hermann Einsele

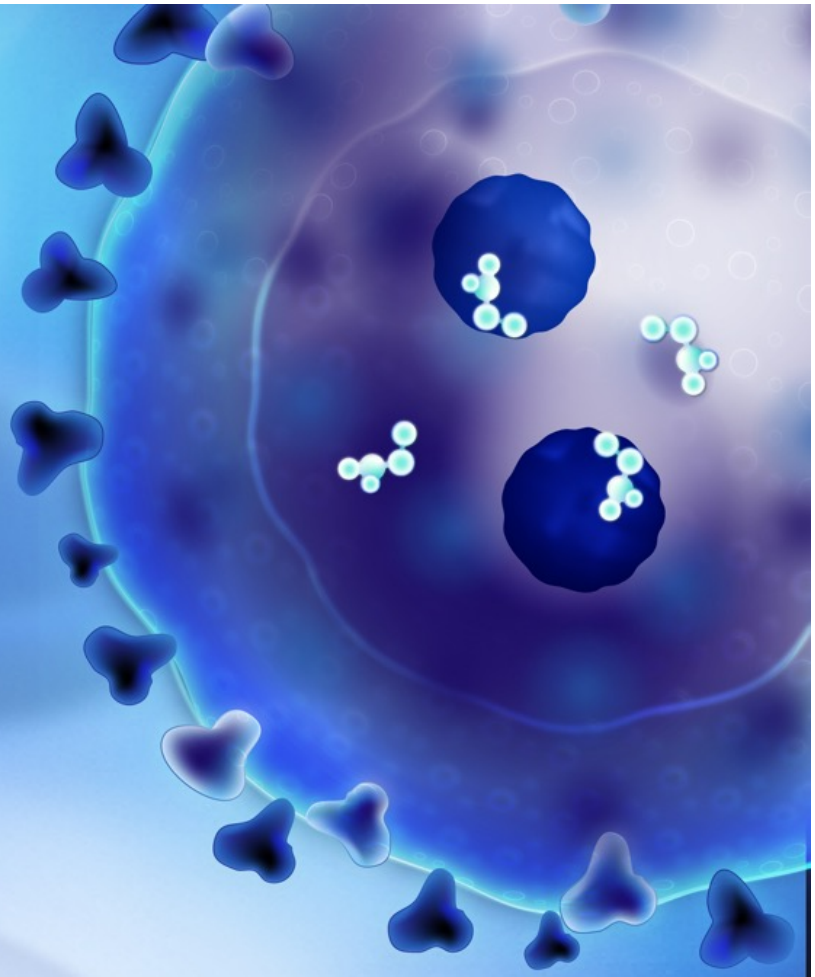
University Hospital Würzburg, Würzburg, Germany

Agenda

Time (EET)	Title	Presenter
16:45–16:50	Introduction	Evangelos Terpos (Chair) *University of Athens, Athens, Greece*
16:50–17:00	Individualised treatment in early relapse in multiple myeloma	Evangelos Terpos
17:00–17:10	Optimising the sequence of novel therapies from early relapse	Hermann Einsele *University Hospital Würzburg, Würzburg, Germany*
17:10–17:15	Q&A and closing remarks	Evangelos Terpos

Individualised treatment in early relapse in multiple myeloma

Evangelos Terpos
University of Athens,
Athens, Greece

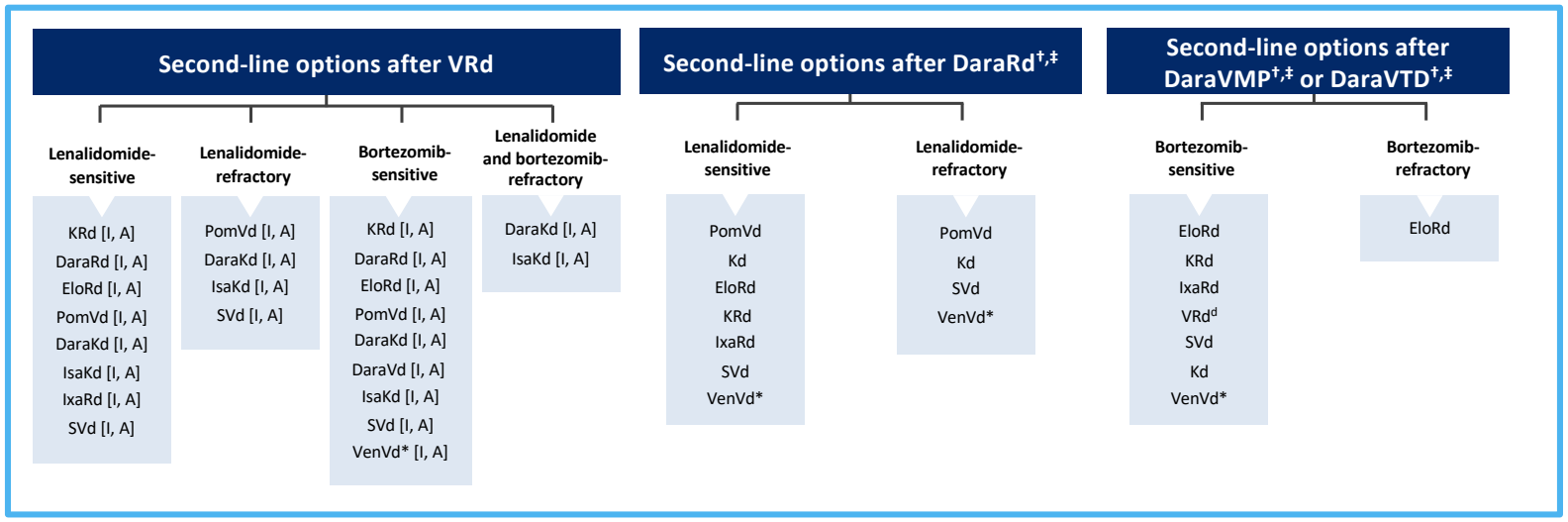


MENARINI group
Stemline
A Menarini Group Company

Disclosures

Company name	Research support	Advisory board	Other (honoraria)
Amgen, GSK, Sanofi, Takeda	X	X	X
Astra/Zeneca, EUSA Pharma, Swixx		X	X
BMS, Pfizer		X	X
Janssen	X		X
Novartis, Antengene			X

2021 EHA-ESMO MM guidelines for initial relapse



There are limited second-line options for difficult-to-treat MM patients who are:

- Anti-CD38-mAb–exposed/refractory
- Lenalidomide-refractory
- PI-naïve

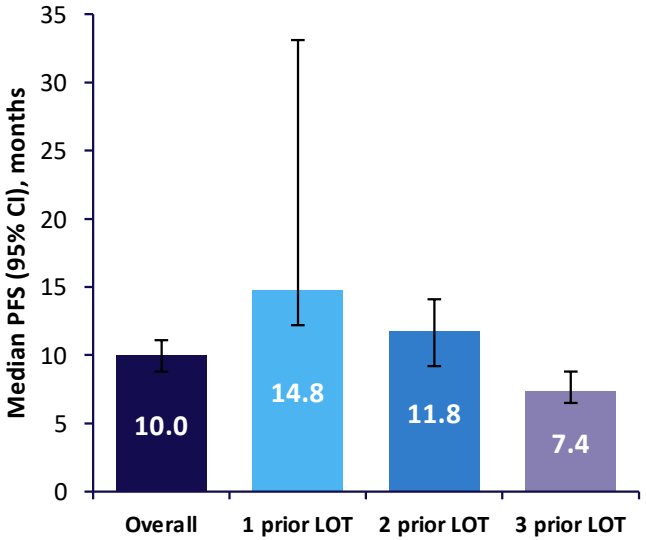
Second-line options recommended by ESMO suggest switching target may be beneficial

*Patients with t(11;14); †Patients who progress while on monthly Dara are considered as Dara-refractory; ‡All recommendations for patients who receive front-line therapy with Dara-based therapies are based on panel consensus as there are no trials evaluating regimens in second-line therapy that include patients refractory or exposed to Dara.
Dara, daratumumab; EHA, European Haematology Association; Elo, elotuzumab; ESMO, European Society for Medical Oncology; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; Kd, carfilzomib/dexamethasone; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; Pom, pomalidomide; Rd, lenalidomide/dexamethasone; S, selinexor; Vd, bortezomib/dexamethasone; Ven, venetoclax; VMP, bortezomib/melphalan/prednisolone; VRd, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

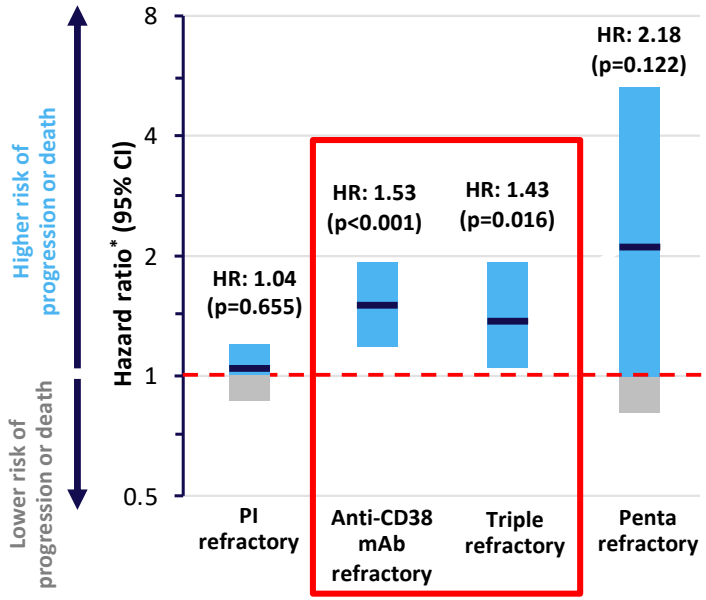
Dimopoulos MA, et al. Ann Oncol 2021;32:309–322.

Lenalidomide-refractory patients treated with one to three prior LOT have poor PFS that generally worsens with each additional LOT

PFS by number of prior LOT after first index treatment in lenalidomide-refractory patients



Prognostic factors for PFS: Refractory status



- Patients with lenalidomide-refractory MM have poor outcomes
- PFS for anti-CD38-mAb-refractory MM is at least as poor as with triple-refractory MM
- Same outcomes were observed for OS

There is a need for novel and effective treatment options for use as early as 2L therapy for lenalidomide-refractory MM

Analysis of individual patient-level data from daratumumab clinical trials: APOLLO, CASTOR, CANDOR, EQUULEUS, ALCYONE, MAIA, GRIFFIN, POLLUX, and CASSIOPEIA.
*Reference for each factor was the absences of the refractory state.
2L, second-line; CI, confidence interval; HR, hazard ratio; LOT, line-of-therapy; mAb, monoclonal antibody; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival.

Yong K, et al. Eur J Cancer 2025;215:115157.

Outcomes in patients when rechallenged with anti-CD38 mAbs

In the EMMY cohort analysis*, 173 patients who initiated a second line of treatment with anti-CD38-based combinations after a first exposure to Dara or Isa were identified and described[1]

Median PFS and OS[1]

Patient group	Median PFS, months (95% CI)	Median OS, months (95% CI)
All CD38-retreated (n=173)	4.7 (3.8–6.5)	16.5 (13.9–21.6)
Anti-CD38 non-refractory	7.2 (3.4–NR)	N/A
Anti-CD38 refractory (n=127)	4.6 (3.7–6.0)	N/A
Anti-CD38-Rd (n=35)	3.8 (1.8–7.2)	25.1

A single-centre analysis described 183 patients with R/R MM who progressed during therapy with a Dara- or Isa-based regimen, then received further therapy[2]

- Patients received anti-CD38 therapy after a median of 2 prior LOTs (range, 1–10)
- **Median PFS on anti-CD38 therapy** for the whole cohort was **6.4 months**
- **Retreatment with anti-CD38** immediately after anti-CD38 relapse resulted in **median PFS of 4.0 months**

Median PFS in post anti-CD38 treatment line by regimen[2†]

Regimen	Median PFS, months
PI-based	6.4
Triplets	6.0
Pomalidomide based	4.5
Anti-CD38 based	4.0

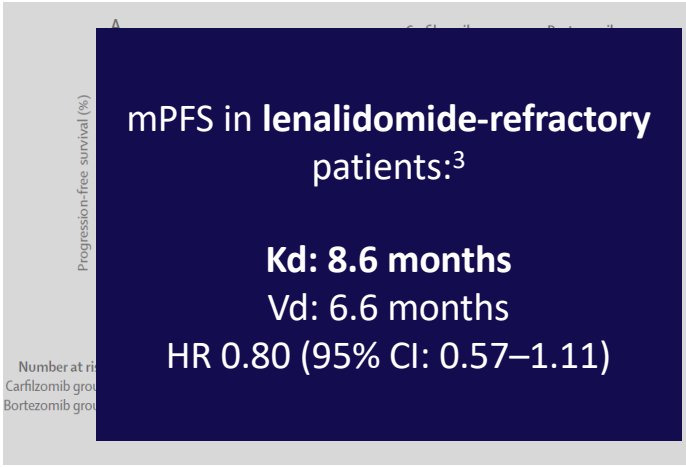
*The EMMY cohort is a non-interventional, prospective dynamic cohort study conducted by the Intergroupe Francophone du Myélome group;
†Only regimens received by ≥20% of ITT patient population.
CD38, cluster of differentiation 38; CI, confidence interval; Dara, daratumumab; Isa, isatuximab; ITT, intention to treat; LOT, line of therapy; mAb, monoclonal antibody; NR, not reached; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide-dexamethasone; R/R MM, relapsed/refractory multiple myeloma.

1. Hulin C et al. Abstract #3174. ASH Annual Meeting 2022;
2. Kastritis E et al. Abstract #3256. ASH Annual Meeting 2022.

Relapse treatment after DRd?

ENDEAVOR[1*]

1–3 prior lines of therapy



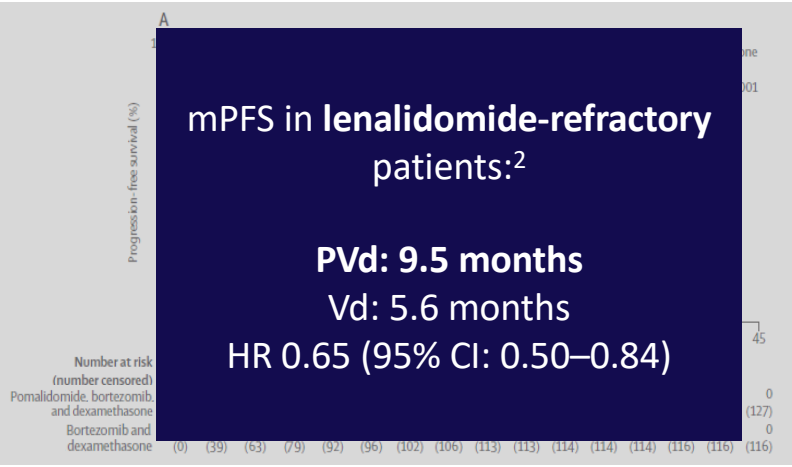
mPFS in **lenalidomide-refractory** patients:[3]

Kd: 8.6 months
Vd: 6.6 months
HR 0.80 (95% CI: 0.57–1.11)

Kd[1]:
- Doublet
- PI
- One new MoA

OPTIMISMM[2†]

1–3 prior lines of therapy, received **prior treatment** with a **lenalidomide-containing regimen** for ≥2 consecutive cycles, not bortezomib refractory



mPFS in **lenalidomide-refractory** patients:[2]

PVd: 9.5 months
Vd: 5.6 months
HR 0.65 (95% CI: 0.50–0.84)

PVd[2]:
- Triplet
- PI
- One new MoA

Multicentric Italian retrospective study[4]

1 or 2 prior lines of therapy, double refractory to lenalidomide and anti-CD38 mAbs

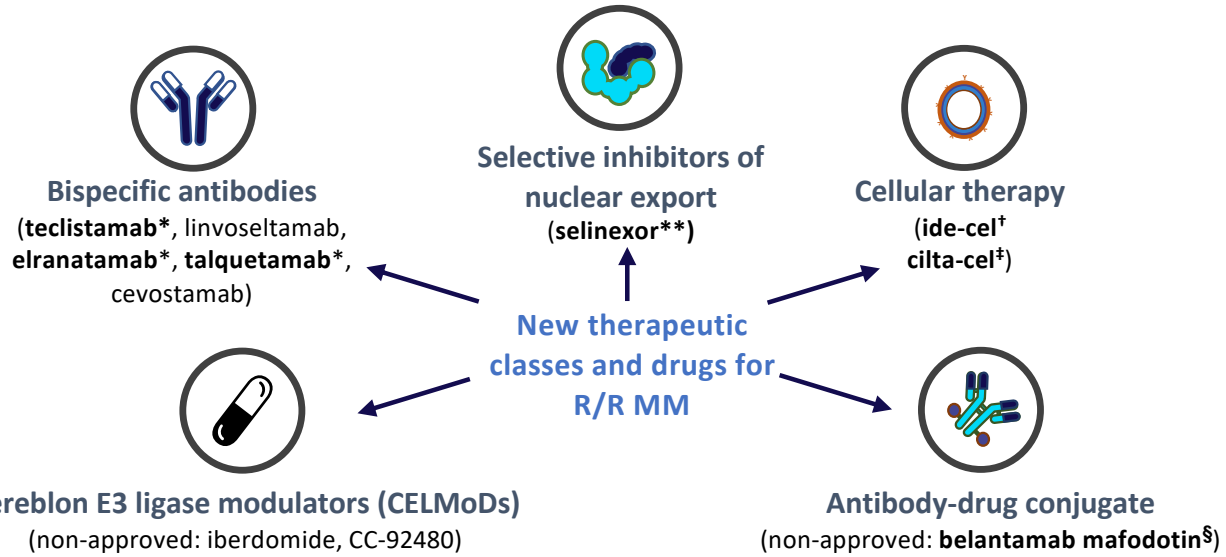
Highlights the need for **more extensive access to therapies**, especially in the setting of **double refractory patients with early relapse** after **exposure to both IMiDS and anti-CD38 mAb** in 1 or 2 line of therapy

Data presented side by side for illustration purposes only – this is not a head-to-head comparison of these studies.
*Median follow-up was 11.9 months (Kd arm) and 11.1 months (Vd arm); †Median follow-up was 15.9 months; ‡After PVd initiation.
CI, confidence interval; CR, complete response; DR, double refractory; DRd, daratumumab/lenalidomide/dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; Kd, carfilzomib/dexamethasone; Len, lenalidomide; mAb, monoclonal antibody; MoA, mechanism of action; (m)PFS, (median) progression-free survival; NE, not estimable; ORR, overall response rate; OS, overall survival; PI, proteasome inhibitor; PR, partial repsonse; PVd, pomalidomide/bortezomib/dexamethasone; VGPR, very good partial response; Vd, bortezomib/dexamethasone.

1. Dimopoulos MA, et al. Lancet Oncol 2016.17:27–38; 2. Richardson PG, et al. Lancet Oncol 2019;20:781–794;
3. Moreau P, et al. Leukemia 2017;31:115–122; 4. Liberatore C, et al. Blood 2024; 144 (Supplement 1): 5153.

Paradigm shift: Novel strategies for R/R MM

Populations with greatest unmet need include those **refractory to lenalidomide or daratumumab** at **early relapse**



Many new therapies are emerging for MM, but challenges remain the same…

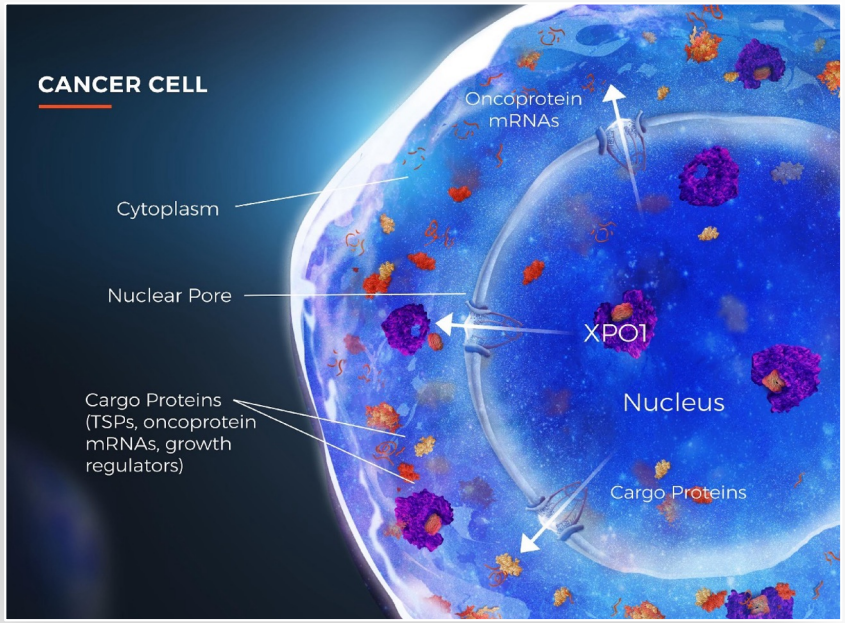
- Patients relapse or become refractory to PIs, IMiDs and anti-CD38 mAbs
- Many patients may not be eligible for ASCT
- No SoC for patients with R/R MM after 1L therapy

It is important to optimise the sequence of drugs to improve patient survival

*EMA approved 4L+ with previous exposure to a PI, IMiD and an anti-CD38 antibody; **EMA approved 2L+; †EMA approved 3L+ with previous exposure to a PI, IMiD and an anti-CD38 antibody; ‡EMA approved 2L+ with previous exposure to a PI and IMiD; §Monotherapy withdrawn from market, combination therapies not yet EMA approved.
1L, first line; ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T cell therapy; EMA, European Medicines Agency; IgG, immunoglobulin G; IMiD, immunomodulatory drug; PI, proteasome inhibitor; R/R MM, relapsed/refractory multiple myeloma; SoC, standard of care.

Davis LN, et al. Cancers. 2021;13:1686; Dimopoulos MA, et al. Ann Oncol 2021;32:309–322.

Selinexor: A first-in-class oral exportin 1 inhibitor, is indicated for adults with R/R MM who have received at least one prior therapy[1,2]



XPO1 overexpression:

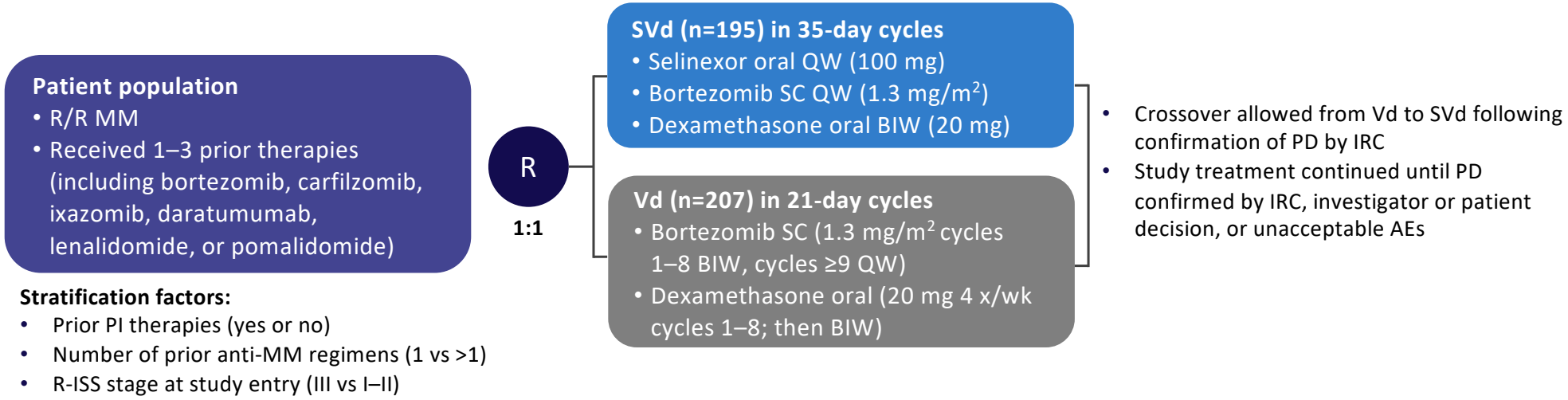
- **Inactivates tumour suppressor proteins[3]**
  - TSPs need to be localised in the nucleus to initiate apoptosis, thereby suppressing tumour growth[4,5]
  - Overexpression of XPO1 results in the functional inactivation of TSPs[2]
- **Enhances proto-oncogene translation[6]**
  - XPO1 overexpression increases nuclear export, and subsequent translation and protein synthesis of multiple eIF4E-bound oncogenic mRNAs
- **Disrupts growth regulation[3,4]**
  - Increased XPO1 expression promotes sustained cellular proliferation through increased cytoplasmic localisation and expression of master growth regulators

ESMO recommendations for daratumumab-pretreated patients include regimens containing **selinexor in combination with bortezomib and dexamethasone**, as well as carfilzomib and pomalidomide-based regimens[7]

ESMO, European Society for Medical Oncology; MM, multiple myeloma; R/R, relapsed/refractory; TSP, tumour suppressor protein; XPO1, exportin 1.

Figure from Karyopharm Therapeutics: https://www.osc.edu/press/karyopharm_therapeutics_scientists_search_for_biomarkers_to_yield_targeted_patient_treatments. Accessed March 2025; 1. Grosicki S, et al. Lancet 2020;396:1563–73; 2. Nexpovio (selinexor) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/nexpovio-epar-product-information_en.pdf; 3. Sun Q, et al. Signal Transduct Target Ther. 2016;1:16010; 4. Tai Y-T, et al. Leukemia 2014;28:155–65; 5. O'Hagan HM, et al. Oncogene 2004;23:5505–12; 6. Culjkovic-Kraljacic B, et al. Cell Rep 2012;2:207–15; 7. Dimopoulos MA, et al. Ann Oncol 2021;32:309–22.

BOSTON: A Phase 3, global, randomised, open label, controlled study in patients with MM who had received 1–3 prior therapies



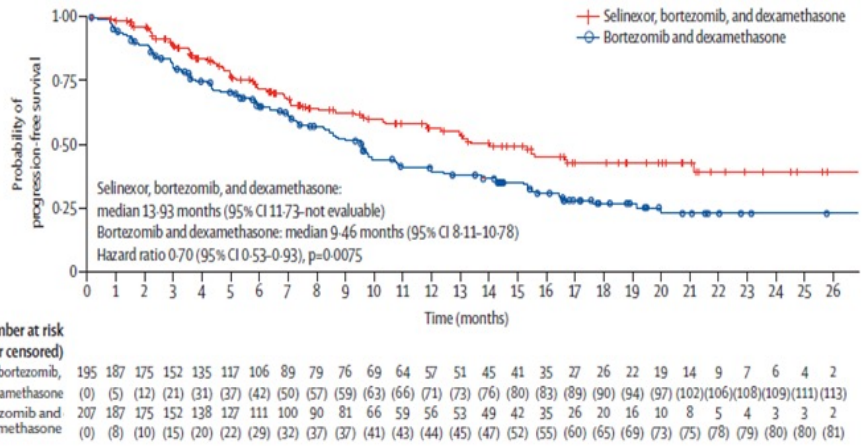
The SVd regimen requires **approximately 40% less bortezomib** than Vd, which entails **37% fewer clinic visits** over the first 6 months of treatment and thus **reduces the burden of care** for patients, providers, and healthcare systems

AE, adverse event; BIW, twice weekly; IRC, Independent Review Committee; PD, progressive disease; PI, proteasome inhibitor; QW, once weekly; R, randomised; R-ISS, Revised International Staging System; R/R MM, relapsed/refractory multiple myeloma; SC, subcutaneous; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

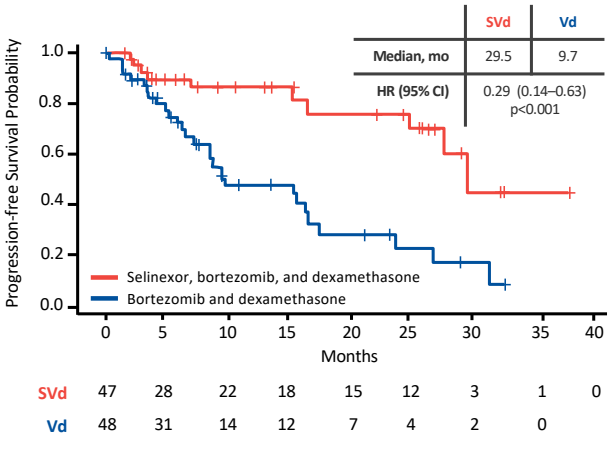
Grosicki S, et al. Lancet 2020;396(10262):1563–1573; https://clinicaltrials.gov/ct2/show/NCT03110562.

BOSTON: Prolonged PFS with SVd vs Vd, including in difficult-to-treat MM populations

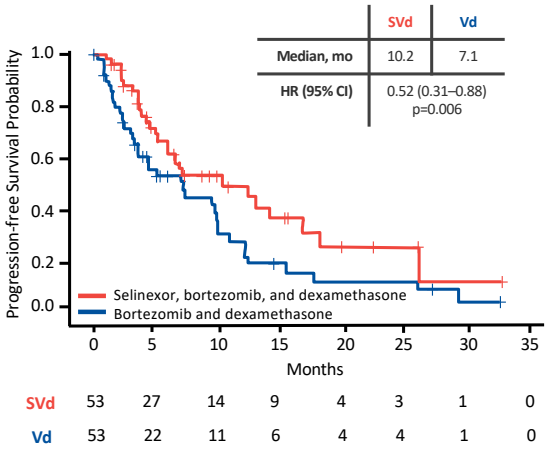
PFS in ITT population[1*]



PFS in PI-naïve population[2†]



PFS in lenalidomide-refractory population[2†]



mOS was **significantly longer** with **SVd vs Vd** in the **lenalidomide-refractory** population (**26.7 vs 18.6 months**; HR 0.53, 95% CI: 0.30–0.95, p=0.015)[2]

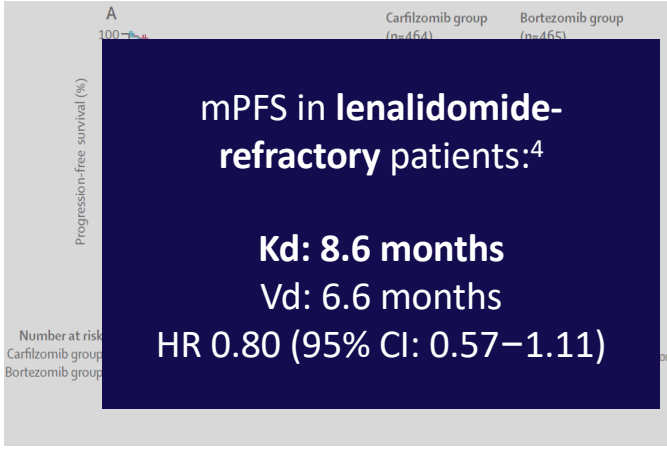
*Median follow-up was 13.2 months (SVd arm) and 16.5 months (Vd arm); †Extended analysis: median follow-up was 28.2 months (SVd arm) and 27.1 months (Vd arm).
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MM, multiple myeloma; mo, month; mOS, median overall survival; PFS, progression-free survival; PI, proteasome inhibitor; HR, hazard ratio; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

1. Grosicki S, et al. Lancet 2020;396(10262):1563–73; 2. Mateos MV, et al. Eur J Haematol 2024;113(2):242–252.

How does SVd fit with the current regimens after DRd relapse?

ENDEAVOR[1*]

1–3 prior lines of therapy



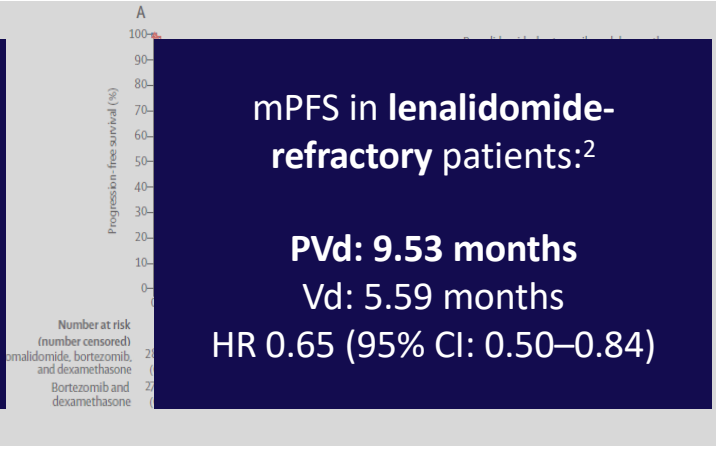
mPFS in **lenalidomide-refractory** patients:[4]

Kd: 8.6 months
Vd: 6.6 months
HR 0.80 (95% CI: 0.57–1.11)

Kd[1]:
- Doublet
- PI
- One new MoA

OPTIMISMM[2†]

1–3 prior lines of therapy, received **prior treatment** with a **lenalidomide-containing regimen** for ≥2 consecutive cycles, not bortezomib refractory



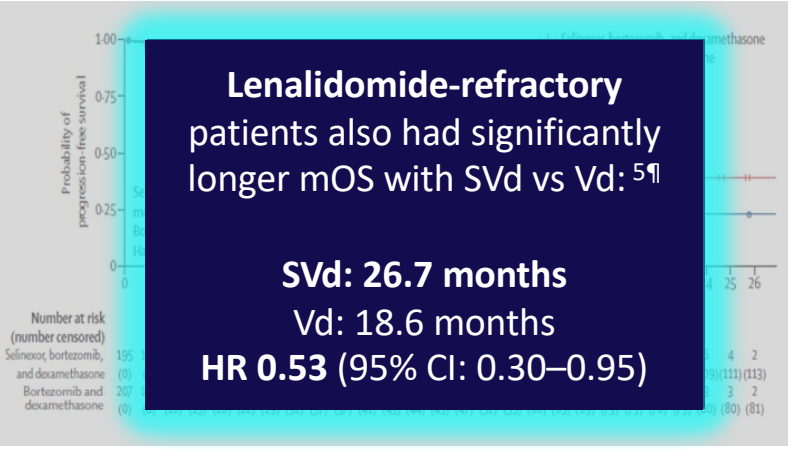
mPFS in **lenalidomide-refractory** patients:[2]

PVd: 9.53 months
Vd: 5.59 months
HR 0.65 (95% CI: 0.50–0.84)

PVd[2]:
- Triplet
- PI
- One new MoA

BOSTON[3‡]

1–3 prior lines of therapy



Lenalidomide-refractory patients also had significantly longer mOS with SVd vs Vd: [5¶]

SVd: 26.7 months
Vd: 18.6 months
HR 0.53 (95% CI: 0.30–0.95)

SelVd[3]:
- Triplet
- PI
- Two new MoAs

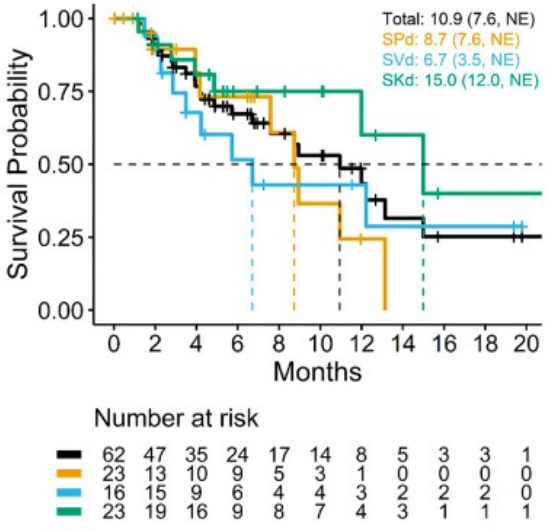
Data presented side by side for illustration purposes only – this is not a head-to-head comparison of these studies.

*Median follow-up was 11.9 months (Kd arm) and 11.1 months (Vd arm); †Median follow-up was 15.9 months; ‡Median follow-up was 13.2 months (SVd arm) and 16.5 months (Vd arm); ¶Extended analysis: median follow-up was 28.2 months (SVd arm) and 27.1 months (Vd arm). CI, confidence interval; DRd, daratumumab/lenalidomide/dexamethasone; HR, hazard ratio; Kd, carfilzomib/dexamethasone; Len, lenalidomide; MoA, mechanism of action; (m)PFS, (median) progression-free survival; (m)OS, (median) overall survival; PI, proteasome inhibitor; PVd, pomalidomide/bortezomib/dexamethasone; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

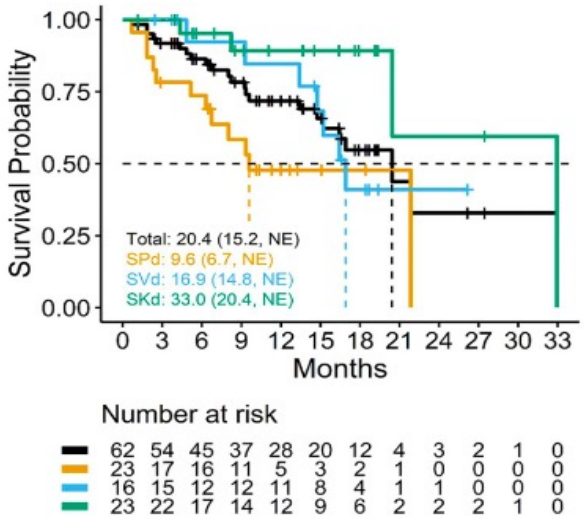
1. Dimopoulos MA, et al. Lancet Oncol 2016.17:27–38; 2. Richardson PG, et al. Lancet Oncol 2019;20:781–94; 3. Grosicki S, et al. Lancet 2020;396(10262):1563–73; 4. Moreau P, et al. Leukemia 2017;31:115–122; 5. Mateos MV, et al. Eur J Haematol 2024;113:242–252.

Efficacy of selinexor-based triplet among patients treated with an αCD38 mAb in a prior line of therapy

Progression-free survival



Overall survival



- Among all patients, **ORR was 58.1%**
- ORR was **highest** in the **SKd cohort** (65.2%)
- Among patients treated with **an αCD38 mAb** in their **most recent prior line of therapy**, **ORR was 56.1%**
- **Clinical benefit rate was 72.6%** among all patients and similar across cohorts

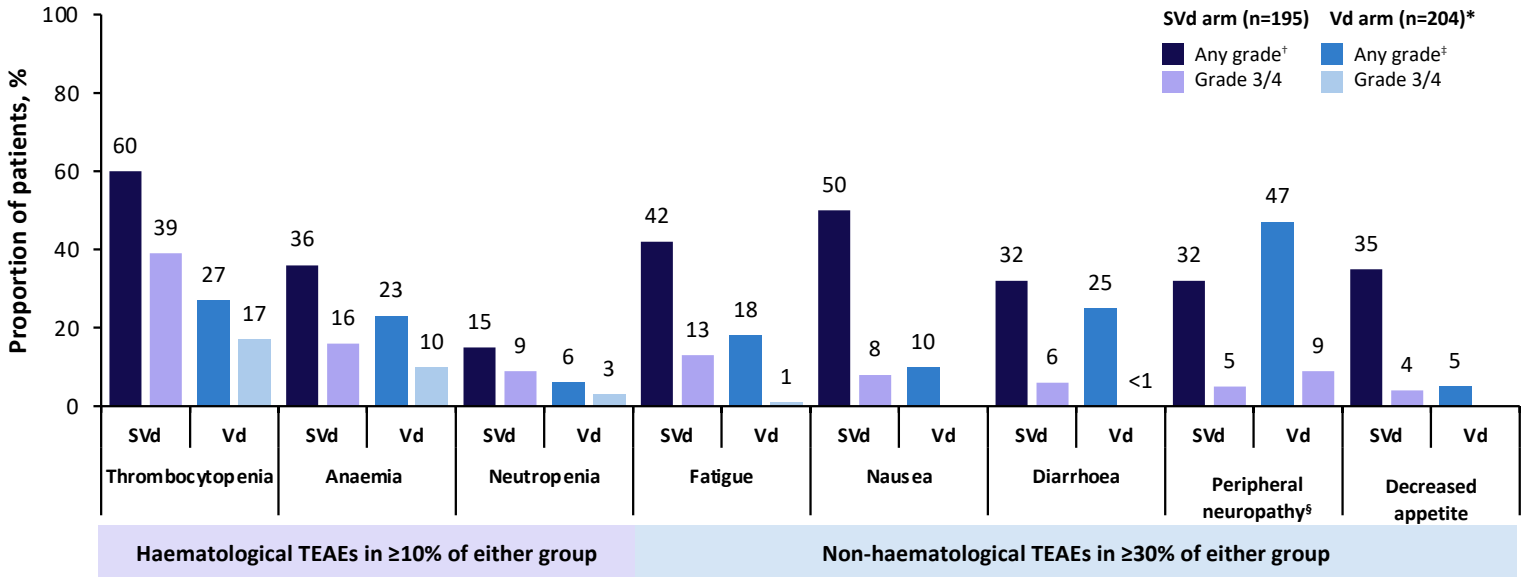
Median of four prior lines of therapy. Median follow-up of 6.9 months for mPFS and 14.5 months for mOS.
CD38, cluster of differentiation 38; mAb, monoclonal antibody; ORR, overall response rate; SKd, selinexor/carfilzomib/dexamethasone; SPd, selinexor/pomalidomide/dexamethasone; SVd, selinexor/bortezomib/dexamethasone.

Schiller GJ, et al. Clin Lymphoma Myeloma Leuk 2023.23(9):e286–e296.e4.

BOSTON: Safety profile

Safety profile was manageable; the most common Grade 3/4 AEs in the SVd arm were thrombocytopenia, fatigue, anaemia, and pneumonia

- AEs may be managed by dose modification and supportive therapeutic measures



*Three patients from this group who did not receive any doses of study drug were excluded from the safety population; †Includes four Grade 5 events: three (2%) cases of pneumonia and one (1%) case of bronchitis; ‡Includes four Grade 5 events: three (1%) cases of pneumonia and one (<1%) case of anaemia; §Includes high-level MedDRA term "peripheral neuropathies NEC".
AE, adverse event; SVd, selinexor/bortezomib/dexamethasone; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; Vd, bortezomib/dexamethasone.

Grosicki S, et al. Lancet. 2020;396:1563–1573.

Management of selinexor-related AEs

A 5-HT_3 receptor antagonist and other antinausea agents should be provided prior to and during treatment with selinexor[1]

Ondansetron
8 mg PO[2] 30–60 minutes prior to each dose and continued for every 8 hours for 2 days following dosing

+

Olanzapine
2.5 mg–5.0 mg PO qhs[2,3]

AND/OR

Aprepitant*
125 mg PO qam day 1 and 80 mg for 2 days each week[2,4,5]

Alternatively, once-weekly oral dose of netupitant 300 mg + palonosetron 0.5 mg[6-8]

One or both antiemetics may be tapered after 6–8 weeks; maintain hydration and caloric intake[4]

Selinexor-related AEs may be managed by dose reductions: BOSTON study[9]

- Overall **dose reductions** were experienced by **73.3% in the SVd** arm and **53.9% in the Vd** arm[9]
- **Dose reductions due to AEs** were experienced by **72.3% in the SVd** arm and **51.0% in the Vd** arm[9]

The **following selinexor dose reduction** recommendations are suggested for patients who experience an adverse reaction† while taking **SVd**[10]

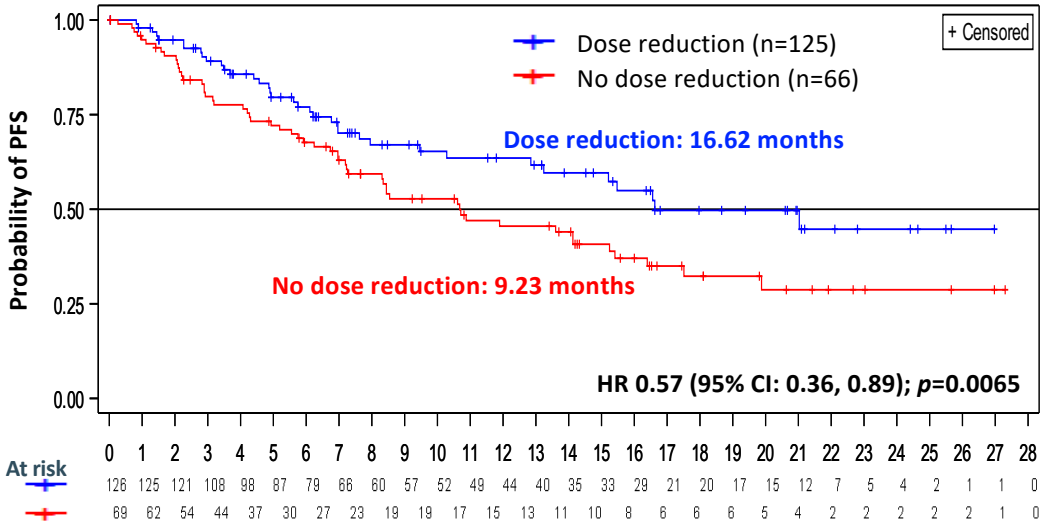
Dose reduction	SVd dose
Recommended starting dose	100 mg once weekly
First dose reduction	80 mg once weekly
Second dose reduction	60 mg once weekly
Third dose reduction	40 mg once weekly
Discontinue if symptoms do not resolve	

The supportive care guidance provided herein are prepared by FORUS Therapeutics Inc. and should not be relied upon as being complete or mandating any particular course of medical care. All treatment decisions are solely at the discretion of the treating physician or healthcare professional. Prophylactic antithrombotic, antimicrobial, or antiemetic agents are not required for treatment with selinexor but may be indicated in specific patients and/or when other anticancer drugs are administered.
*Using dexamethasone together with aprepitant and/or netupitant + palonosetron may increase the effects of dexamethasone; if using either of these agents, the dose of dexamethasone may need to be reduced[5]; †Side effects related to selinexor are largely dosage and schedule dependent and may be mitigated with prophylactic antiemetics and standard monitoring with dose adjustments as needed.
AE, adverse event; PO, by mouth; qam, every morning; qhs, every night; SVd, selinexor/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone..

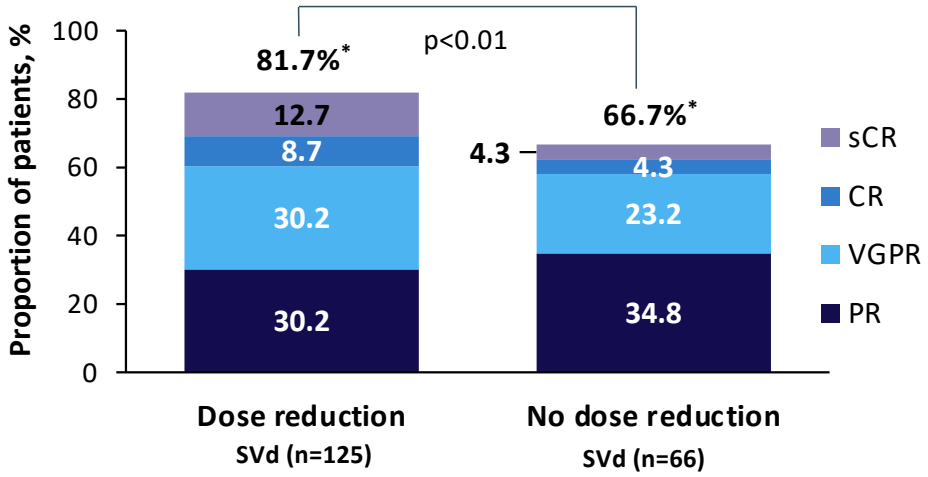
1. Selinexor. Product monograph. FORUS Therapeutics Inc. May 2022; 2. Gavriatopoulou M, et al. Leukemia. 2020;34:2430-2440; 3. Olanzapine. Product monograph. Mylan Pharmaceuticals. February 2017; 4. Mikhael J, et al. Clin Lymphoma Myeloma Leuk. 2020;20:351-357; 5. Aprepitant. Product monograph. Merck Canada Inc. January 2014; 6. Netupitant and palonosetron. Product monograph. Knight Therapeutics Inc. November 2022; 7. Magen H, et al. Clin Lymphoma Myeloma Leuk. 2020;20:e947-e955; 8. Lacey J, et al. Can Hematol Today. 2022;1(suppl 11); 9. Grosicki S, et al. Lancet. 2020;396:1563-1573; 10. Nexpovio (selinexor) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/ nexpovioepar-product-information_en.pdf. .

BOSTON: PFS and ORR in patients with selinexor dose reductions treated with SVd

PFS by dose reduction in patients in the SVd arm



ORR by dose reduction of selinexor in the SVd arm



- These subgroup analyses were exploratory in nature, not included in the study objectives, and do not control for type 1 error
- The analyses were not powered or adjusted for multiplicity to assess efficacy outcomes across these subgroups

*ORR is the proportion of patients who have a PR or better, before IRC-confirmed PD or initiating a new multiple myeloma treatment or crossover.
CR, complete response; HR, hazard ratio; IRC, independent review committee; mPFS, median progression-free survival; ORR, overall response rate; PD, progressive disease; sCR, stringent complete response; SVd, selinexor/bortezomib/dexamethasone; VGPR, very good partial response.

Jagannath S, et al. Abstract #3793; poster presented at ASH 2021.

Second-line anti-myeloma therapy

Anti-CD38 naïve or sensitive and

Lenalidomide-sensitive or naïve & bortezomib refractory

Preferred regimens:
DaraRd [I, A]
DaraKd [I, A]
IsaKd [I, A]
BelaPd* [I, A]

Other approved indications:
KRd [I, A]
IxaRd [I, A]
EloRd [I, A]

*in lenalidomide-exposed patients only

Lenalidomide-sensitive or naïve & bortezomib sensitive

Preferred regimens:
DaraRd [I, A]
DaraKd [I, A]
IsaKd [I, A]
BelaVd [I, A]
BelaPd* [I, A]

Other approved indications:
KRd [I, A]
IxaRd [I, A]
EloRd [I, A]
SVd [I, A]

PomVd* or DaraVd may be used in the absence of BelaPd* or BelaVd, respectively [panel consensus: I, A]

*in lenalidomide-exposed patients only

Lenalidomide-refractory & bortezomib sensitive

Preferred regimens:
Cilta-cel [I, A]
DaraKd [I, A]
IsaKd [I, A]
BelaPd [I, A]

Other approved indications:
BelaVd [I, A]
DaraPd [I, A]
SVd [I, A]

PomVd or DaraVd may be used in the absence of BelaPd or BelaVd, respectively [panel consensus: I, A]

Lenalidomide & bortezomib refractory

Cilta-cel [I, A]
BelaPd [I, A]
DaraKd [I, A]
IsaKd [I, A]
DaraPd [II, B]

Anti-CD38 refractory and

Lenalidomide-refractory & bortezomib sensitive

Preferred regimens:
Cilta-cel [I, A]
BelaPd [I, A]

Other approved indications:
SVd [II, C]
Kd [panel consensus; V, C]
BelaVd [panel consensus; V, C]

PomVd may be used only in the absence of BelaPd [panel consensus: I, A]

Lenalidomide & bortezomib refractory

Preferred regimens:
Cilta-cel [I, A]
BelaPd [I, A]

Lenalidomide sensitive

Preferred regimens:
BelaPd [I, A]

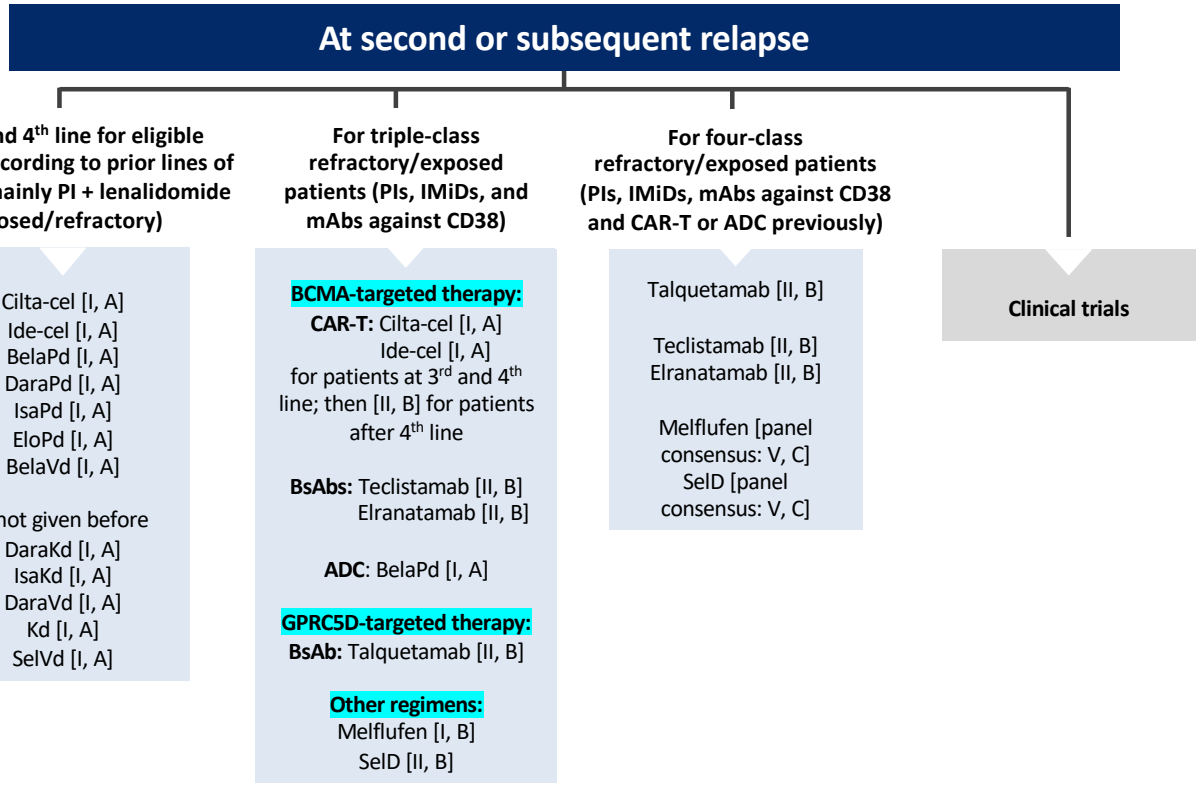
Other approved indications:
BelaVd [V, C]
KRd [V, C]
IxaRd [V, C]
EloRd [V, C]
SVd [II, C]
Kd [V, C]

PomVd may be used in the absence of BelaPd [panel consensus: I, A]

Bela, belantamab mafodotin; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; Kd, carfilzomib/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; Pd, pomalidomide/dexamethasone; PomVd, pomalidomide/bortezomib/dexamethasone; R, lenalidomide; Rd, lenalidomide/dexamethasone; S, selinexor; Vd, bortezomib/dexamethasone.

Dimopoulos MA, Terpos E, et al. Nat Rev Clin Oncol 2025 (under minor revision).

Anti-myeloma therapy at second or subsequent relapse



ADC, antibody-drug conjugate; Bela, belantamab mafodotin; BCMA, B-cell maturation antigen; BsAb, bispecific monoclonal antibody; CAR T, chimeric antigen receptor T-cell; cilta-cel, ciltacabtagene autoleucel; D, dexamethasone; Dara, daratumumab; Elo, elotuzumab; ide-cel, idecabtagene vicleucel; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; Kd, carfilzomib/dexamethasone; Pd, pomalidomide/dexamethasone; PomVd, pomalidomide/bortezomib/dexamethasone; R, lenalidomide; Rd, lenalidomide/dexamethasone; S, selinexor; Vd, bortezomib/dexamethasone.

Dimopoulos MA, Terpos E, et al. Nat Rev Clin Oncol 2025 (under minor revision).

Summary

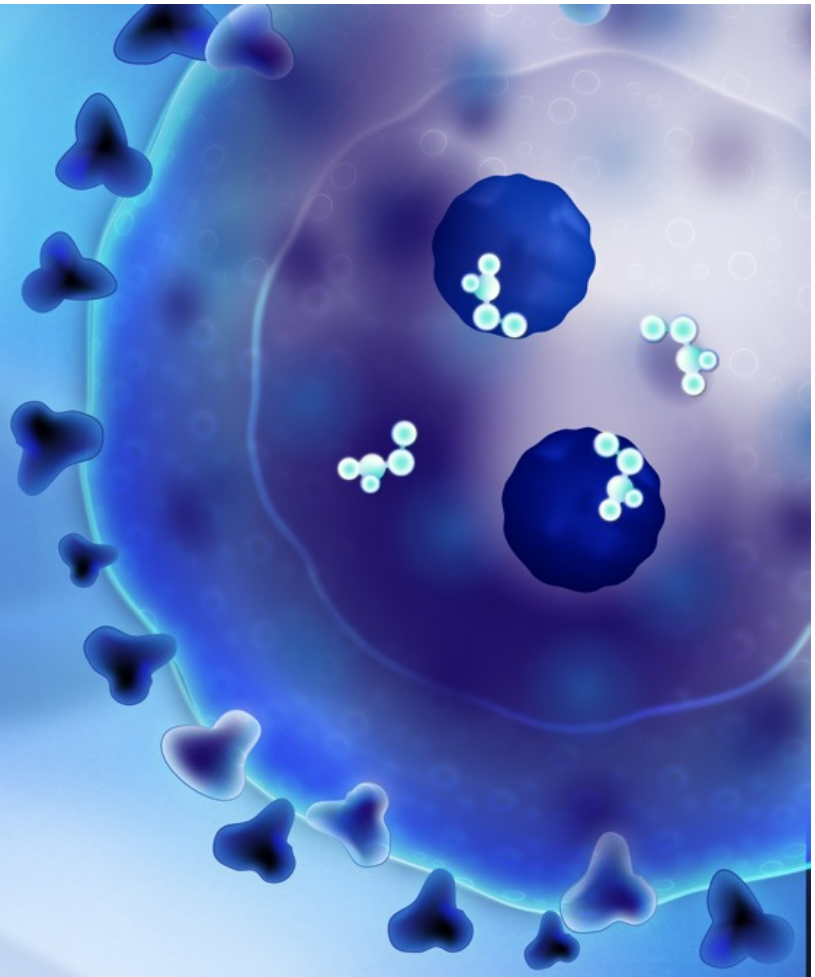
- Although therapeutic advances in MM have improved outcomes, this has generated a wide range of patient profiles at early relapse
- There is a need for **new targets/new drugs with a different MoA**
- Many novel immunotherapies for R/R MM, including CAR-T cell therapy, bispecific antibodies and ADCs, are coming to earlier lines of treatment
- **Selinexor** is a first-in-class, oral XPO1 inhibitor **with a unique MoA**
  - SVd may be a suitable treatment option for early relapsed patients previously treated with lenalidomide and daratumumab, as it offers a **double MoA switch**
- In the real-world setting, SVd is easy to manage with dose reductions and prophylactic use of drugs, resulting in good efficacy outcomes

To improve patient survival rates, we need to better understand the optimal sequencing of these novel therapies

ADC, antibody-drug conjugates; CAR T, chimeric antigen receptor T-cell; MM, multiple myeloma; MoA, mechanism of action; R/R, relapsed/refractory; SVd, selinexor/bortezomib/dexamethasone; XPO1, exportin 1.

Optimising the sequence of novel therapies from early relapse

Hermann Einsele
University Hospital Würzburg,
Würzburg, Germany



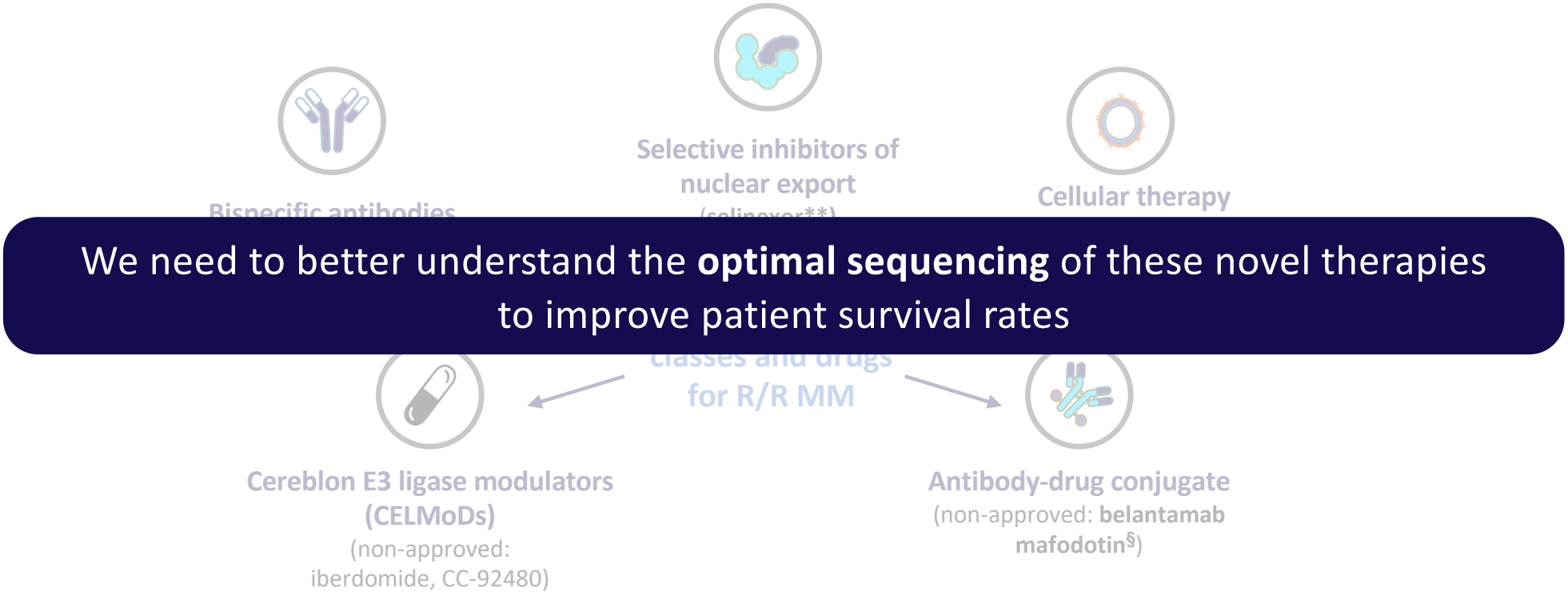
MENARINI group

Stemline
A Menarini Group Company

Disclosures

Company name	Research support	Advisory board	Other (honoraria)
BMS/Celgene	x	x	x
Janssen	x	x	x
Amgen	x	x	x
GSK	x	x	x
Sanofi	x	x	x
Novartis	x	x	x
Takeda		x	x
Roche		x	x

Paradigm shift: Novel strategies for R/R MM



*EMA approved 4L+ with previous exposure to a PI, IMiD and an anti-CD38 antibody; **EMA approved 2L+; †EMA approved 3L+ with previous exposure to a PI, IMiD and an anti-CD38 antibody; ‡EMA approved 2L+ with previous exposure to a PI and IMiD; §Monotherapy withdrawn from market, combination therapies not yet EMA approved.
CAR-T, chimeric antigen receptor T cell therapy; EMA, European Medicines Agency; IMiD, immunomodulatory drug; L, line; MM, multiple myeloma; PI, proteasome inhibitor; R/R, relapsed/refractory.

Davis LN, et al. Cancers 2021;13:1686.

Factors that may influence the use and success of T cell-based therapies

Patient selection[1,2]

- Age
- Fitness
- Prior therapies
- Comorbid diseases
- Myeloma characteristics
- Organ function
- Turnaround time
- Institutional familiarity
- Logistics

Therapy-related drug selection factors[3–5]

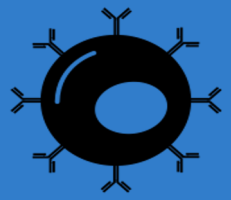
CAR-T manufacturing process

Time from T cell collection to CAR-T administration is approximately ~6−>8 weeks

ICANS/CRS management for CAR-T and bispecifics

Infection rates and other specific toxicities

T-cell fitness & T-cell exhaustion[1]



Advanced disease and **previous therapies** can result in T-cell exhaustion, which may be associated with non-response and relapse

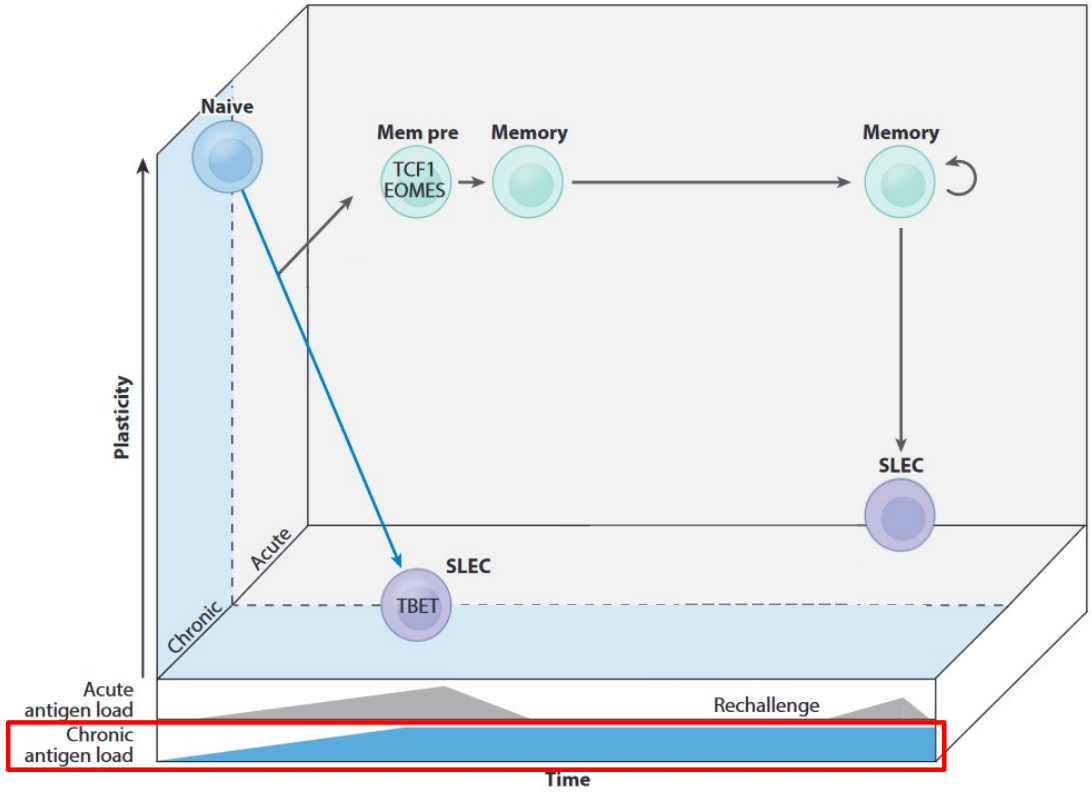
BCMA expression[6]

BCMA therapies exhaust BCMA production, which is linked to poor responses when **sequencing** with other BCMA therapies

BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome.

1. Binder AF, et al. Front Immunol 2023:14:1275329; 2. Jaggers, et al. Journal of Geriatric Oncology 2021;235–238; 3. Rendo MJ, et al. Blood Lymphat Cancer 2022:12:119–136; 4. Dejenie TA, et al. Hum Vaccin Immunother 2022;18:2114254; 5. Sterner RC, Sterner RM. Blood Cancer J 2021;11:69; 6. Zhou X, et al. Haematologica 2023;108:958–968.

T-cell differentiation / exhaustion

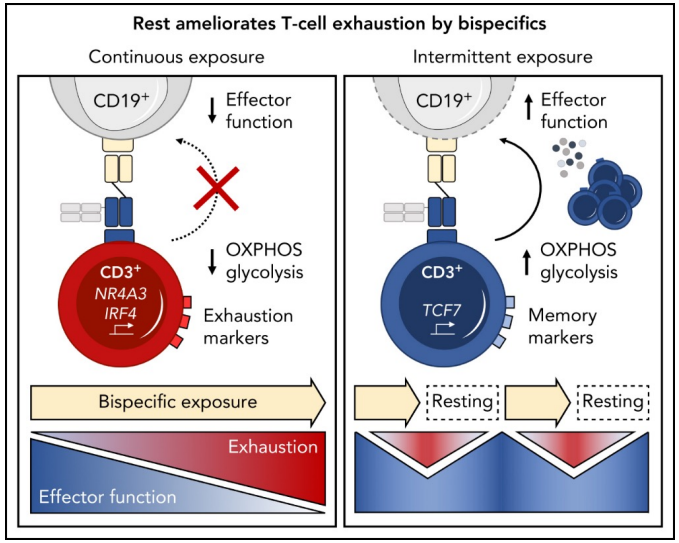


Int, intermediate; mem pre, memory precursor; pre, precursor; prog, progenitor; SLECs, short-lived effector cells; TCF1, T-cell factor 1; Term, terminally; Tex, exhausted T cell; TOX, thymocyte selection–associated HMG box protein.

Baessler A, Vignali DAA. Annu Rev Immunol 2024;42:179–206.

Treatment-free intervals may counteract T-cell exhaustion

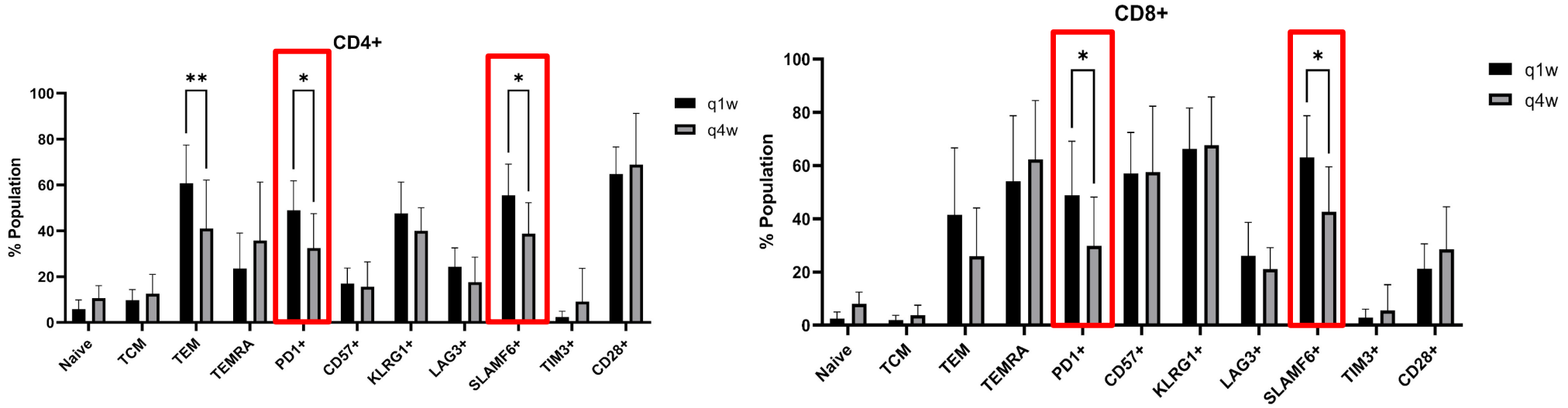
- Most bispecific antibody therapies have been developed with **continuous therapy schedules**, which can be detrimental to T-cell fitness[1,2]
- Accumulating data suggest that **treatment-free intervals** can be beneficial in functional and transcriptional T-cell rejuvenation[2]



- Continuous exposure to a CD19xCD3 bispecific molecule induces T-cell exhaustion[2]
- Treatment-free intervals transcriptionally reprogramme and functionally reinvigorate T cells[2]

1. Binder AF, et al. Front Immunol 2023:14:1275329; 2. Philipp N, et al. Blood 2022:140:1104–1118.

The impact of treatment-free intervals on T-cell exhaustion with BCMA bispecific antibodies

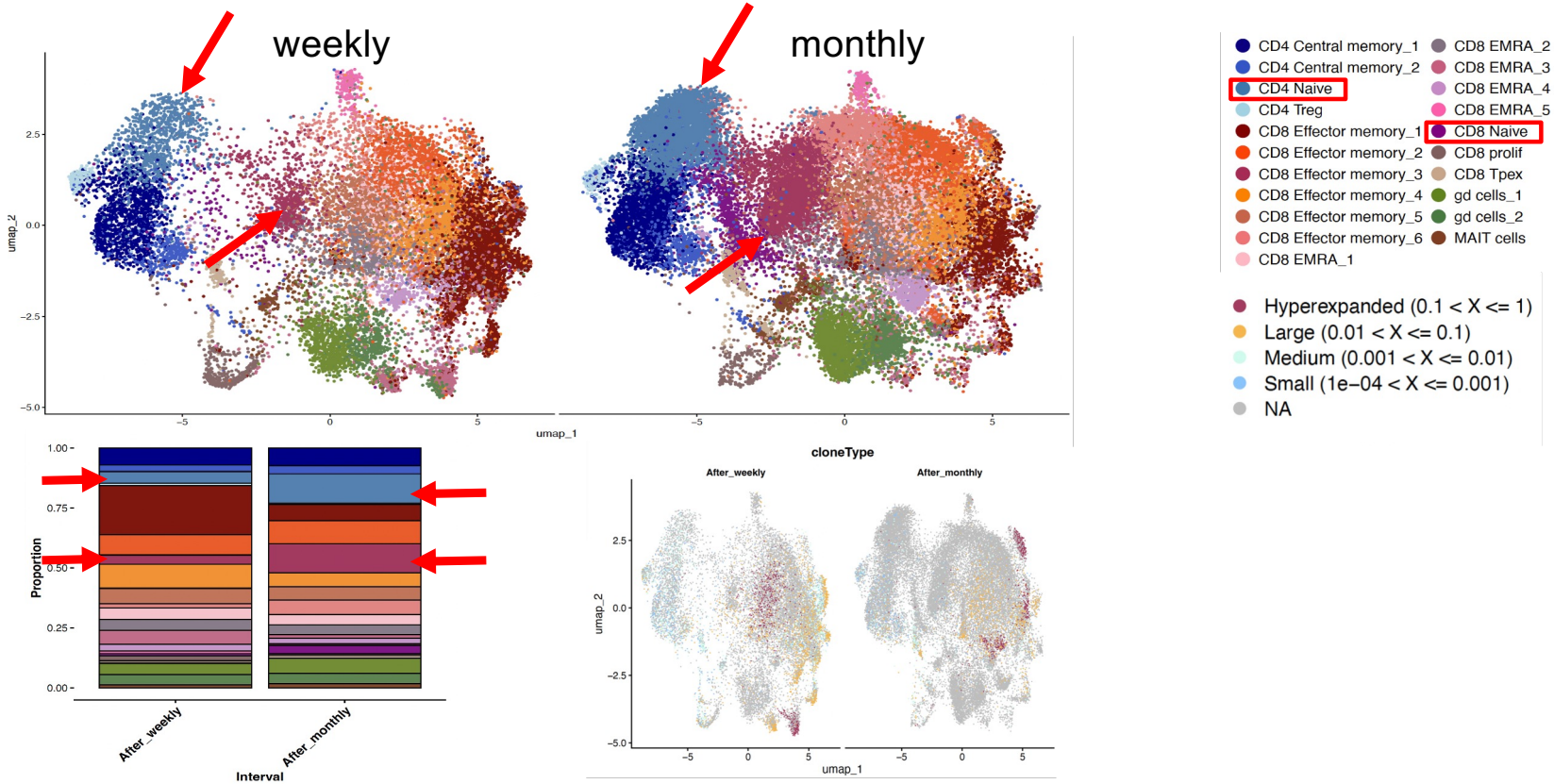


Flow cytometry analysis of T-cell subsets demonstrate a significant decline in exhaustion markers in monthly treated patients

BCMA, B-cell maturation antigen; q1w, once weekly; q4w, every 4 weeks.

Eisele F, et al. Abstract #1938; poster presented at ASH 2023.

Flow analysis and CITE-seq reveal an increase in naïve T cells, suggesting a restoration of T-cell homeostasis



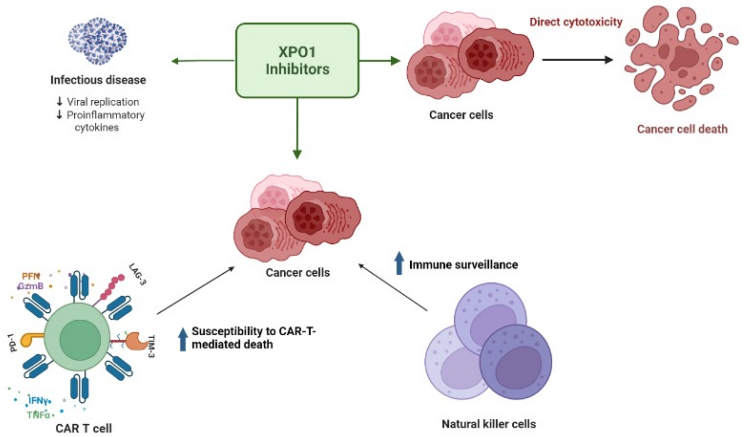
CITE-seq, cellular indexing of transcriptomes and epitopes by sequencing; gd, gamma delta; MAIT, mucosal-associated Invariant T; NA, not applicable; prolif, proliferation; Tpex, progenitor exhausted T cell; Treg, regulatory T cell.

Eisele F, et al. Abstract #1938; poster presented at ASH 2023.

Selinexor, an XPO1 inhibitor, has potential to promote T-cell fitness and reduce T-cell exhaustion

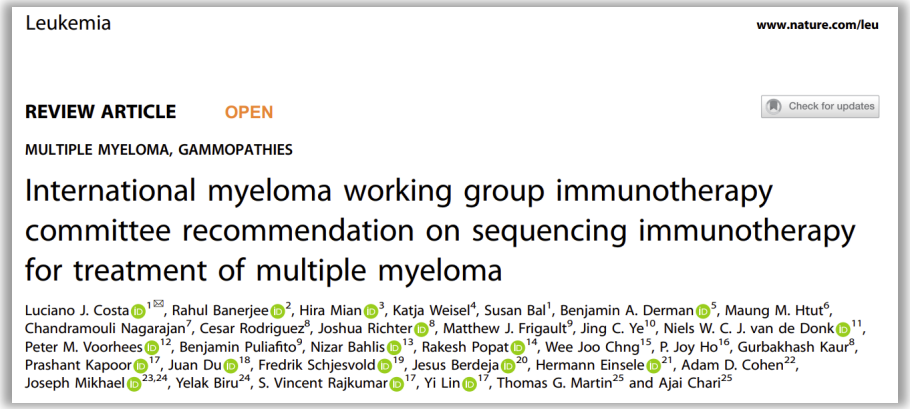
XPO1 inhibitors:[1]

- Have direct cytotoxic effects on tumour cells
- Decrease inflammation in infectious disease
- May facilitate a favourable immune microenvironment for effector T cells to combat T-cell exhaustion



*The **XPO1 inhibitors** selinexor and eltanexor have been shown to **reduce T-cell exhaustion** in cell lines and animal models, suggesting their potential role in revitalising these key effector cells*[1]

*"In addition to direct cytotoxicity against malignant cells, **XPO1 inhibitors may modulate the immune microenvironment to promote T-cell fitness** and **reduce markers of T-cell exhaustion**"*[2]


Leukemia www.nature.com/leu

REVIEW ARTICLE OPEN

Check for updates

MULTIPLE MYELOMA, GAMMOPATHIES

International myeloma working group immunotherapy committee recommendation on sequencing immunotherapy for treatment of multiple myeloma

Luciano J. Costa[1✉], Rahul Banerjee[2], Hira Mian[3], Katja Weisel[4], Susan Bal[1], Benjamin A. Derman[5], Maung M. Htut[6], Chandramouli Nagarajan[7], Cesar Rodriguez[8], Joshua Richter[8], Matthew J. Frigault[9], Jing C. Ye[10], Niels W. C. J. van de Donk[11], Peter M. Voorhees[12], Benjamin Puliafito[9], Nizar Bahlis[13], Rakesh Popat[14], Wee Joo Chng[15], P. Joy Ho[16], Gurbakhash Kaur[8], Prashant Kapoor[17], Juan Du[18], Fredrik Schjesvold[19], Jesus Berdeja[20], Hermann Einsele[21], Adam D. Cohen[22], Joseph Mikhael[23,24], Yelak Biru[24], S. Vincent Rajkumar[17], Yi Lin[17], Thomas G. Martin[25] and Ajai Chari[25]

1. Binder AF, et al. Front Immunol 2023:14:1275329; 2. Costa LJ, et al. Leukemia 2025;39:543–554.

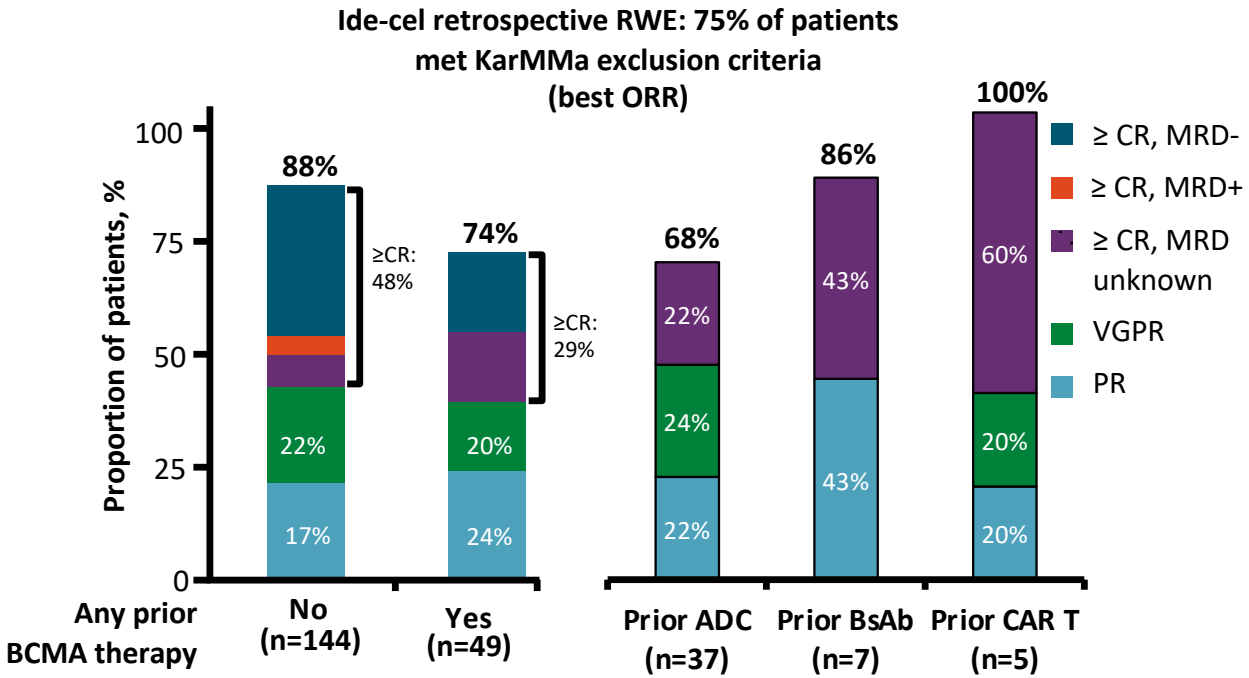
BCMA overexpression

- The **overexpression** and **activation** of **BCMA** are associated with progression of MM in preclinical models and humans, which makes it an **attractive therapeutic target**
- Targeting BCMA with **CAR-T cells, bispecific T-cell engagers or ADCs** has significantly advanced the treatment of R/R MM
- **Repeated treatments** with these agents appear to be possible, but soon, **enhanced benefit and improved outcome** may be optimised by their use in **better sequencing** or at earlier stages…

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MM, multiple myeloma; R/R relapsed/ refractory.

Kleber M, et al. J Clin Med 2021;10:4088; Shah, N, et al. Leukemia 2020;34, 985–1005; Tai YT, et al. Expert Opin Biol Ther 2019;19:1143−1156; Harousseau JL, et al. Blood 2023;141:211–212.

Outcomes of CAR T-cell therapy after prior BCMA-DT



It is better:

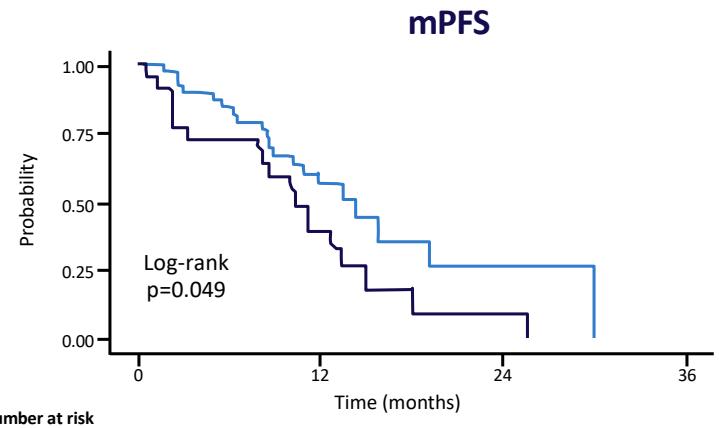
- **NO PRIOR BsAb to CAR-T cells**
- **NO PRIOR CAR-T cells to CAR-T cells same target**
- **NO PRIOR ADC to BCMA-CAR-T cells (e.g., ide-cel)**

ADC, antibody–drug conjugate; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CR, complete response; ide-cel, idecabtagene vicleucel; mAb, monoclonal antibody; MR, minimal response; MRD, measurable residual disease; ORR, overall response rate; PR, partial response; RWE, real-world evidence; VGPR, very good partial response.

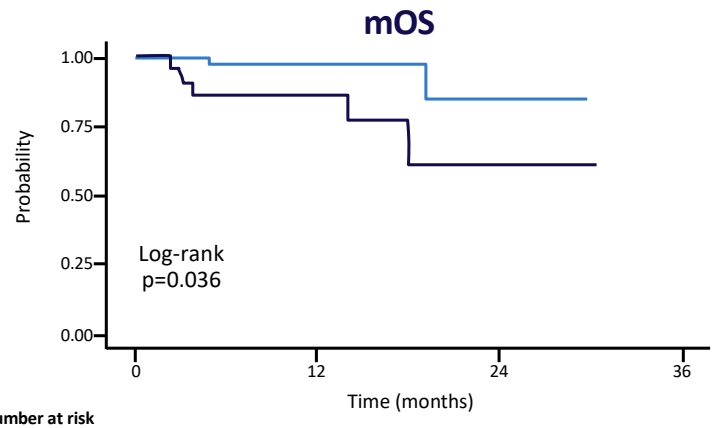
Ferreri CJ, et al. Blood Cancer J 2023;13:117.

Outcomes of CAR T-cell therapy after prior belantamab exposure

Efficacy outcomes with Ide-cel



Number at risk				
Prior BCMA therapy - No	39	15	2	0
Prior BCMA therapy - Yes	22	7	1	0



Number at risk				
Prior BCMA therapy - No	39	25	3	0
Prior BCMA therapy - Yes	22	17	2	0

Prior exposure to belantamab adversely impacted efficacy outcomes with ide-cel therapy

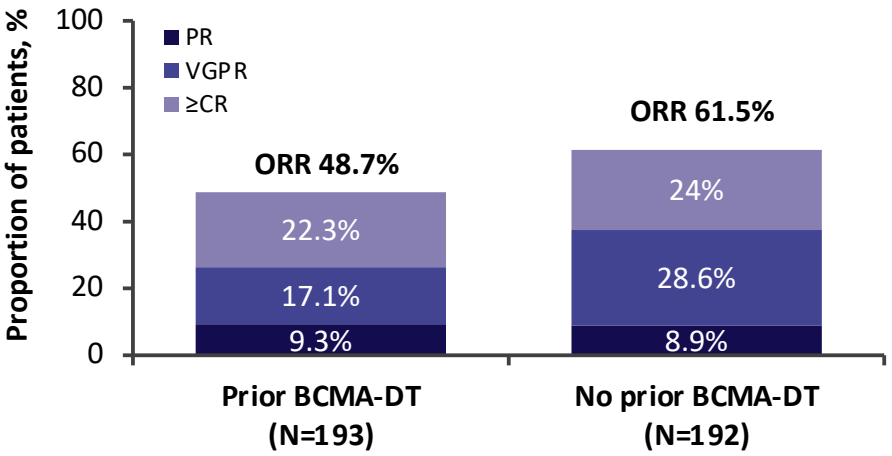
- Patients with **prior exposure to belantamab** had significantly **inferior median PFS** (p=0.049) and **median OS** (p=0.036) vs those without prior exposure to belantamab
- Among patients who received belantamab, **median PFS was significantly lower in patients who had a partial response or better with belantamab** vs patients with no response (p=0.014)
- **PFS and OS did not differ significantly** based on the **time from the last dose of belantamab to the ide-cel infusion**

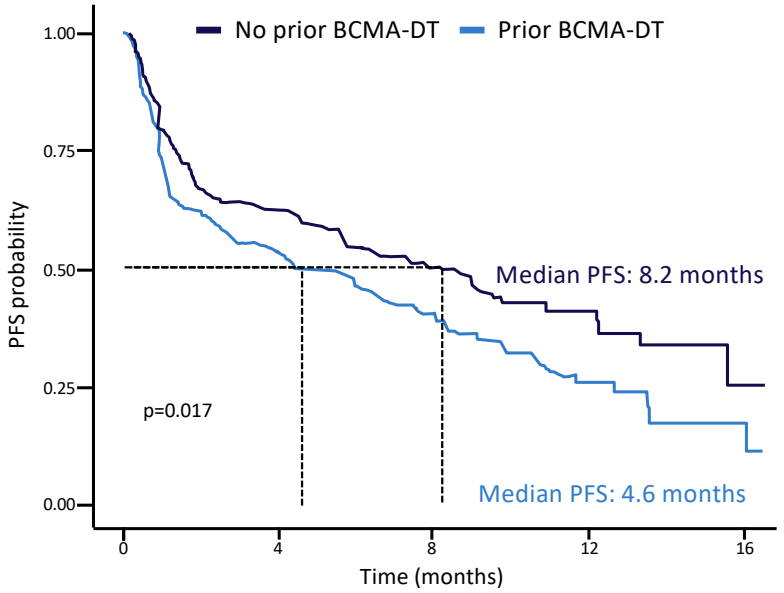
BCMA, B-cell maturation antigen; m, median; OS, overall survival; PFS, progression-free survival.

Lal BM, et al. Abstract #3789; poster presented at ASH 2024.

Outcomes of bispecific antibodies after prior BCMA-DT

Efficacy outcomes with teclistamab





- The prior BCMA-DT cohort had **worse ORR** (p=0.012) **and ≥VGPR** (p=0.009), but **similar ≥CR rates** (p=0.78) compared with those without prior BCMA-DT
- In MVA there was a strong signal for worse ORR in the prior BCMA-DT cohort; however, prior BCMA-DT was not independently associated with the likelihood of achieving response (HR 0.64, 95% CI: 0.41–1.01; p=0.057)

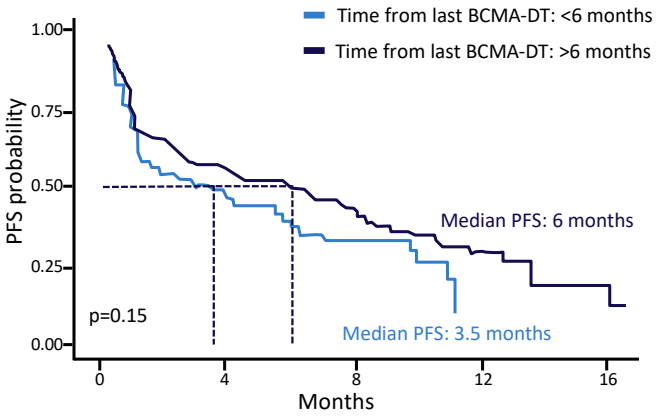
Teclistamab efficacy is strongly affected by prior exposure to BCMA-DT

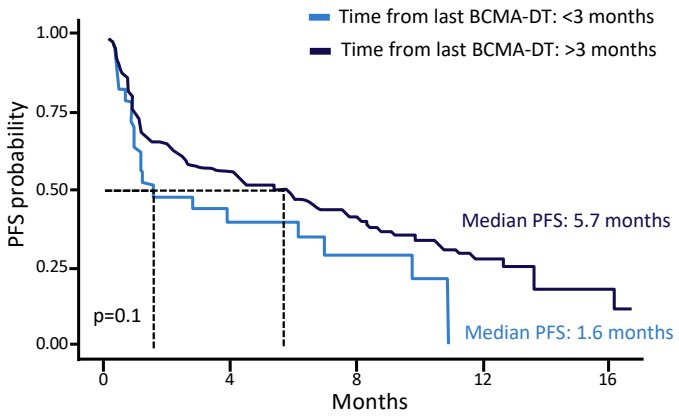
BCMA, B-cell maturation antigen; CR, complete response; DoR, duration of response; DT: directed therapy; HR, hazard ratio; MVA: multivariate analysis; ORR, overall response rate; PFS, progression-free survival; PR, partial response; VGPR, very good partial response.

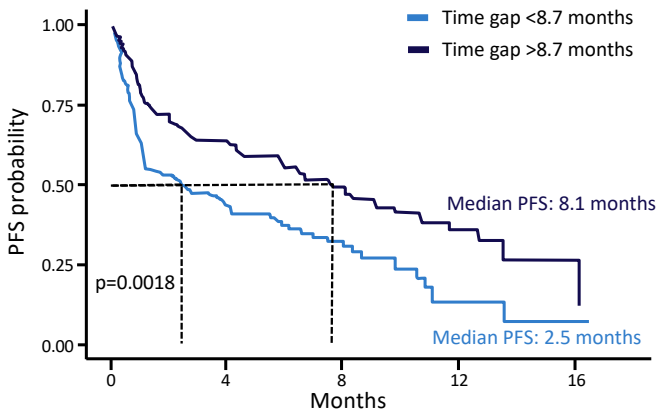
Dima D, et al. Abstract #897; oral presentation at ASH 2024.

Outcomes of bispecific antibodies after prior BCMA-DT

PFS outcomes with teclistamab stratified by timing of prior BCMA-DT







The analysis showed that the **optimal cut-off for time** from the last **BCMA-DT exposure to teclistamab initiation** was **8.7 months**

Patients with >8.7 months between last exposure to prior BCMA-DT and teclistamab initiation had a **superior median PFS with teclistamab** (8.1 months, 95% CI: 4.6–11.7) vs patients with <8.7 months from last prior BCMA-DT exposure (2.5 months, 95% CI: 1.1–5.7), p=0.001

BCMA, B-cell maturation antigen; CI, confidence interval; DT, directed therapy; PFS, progression-free survival.

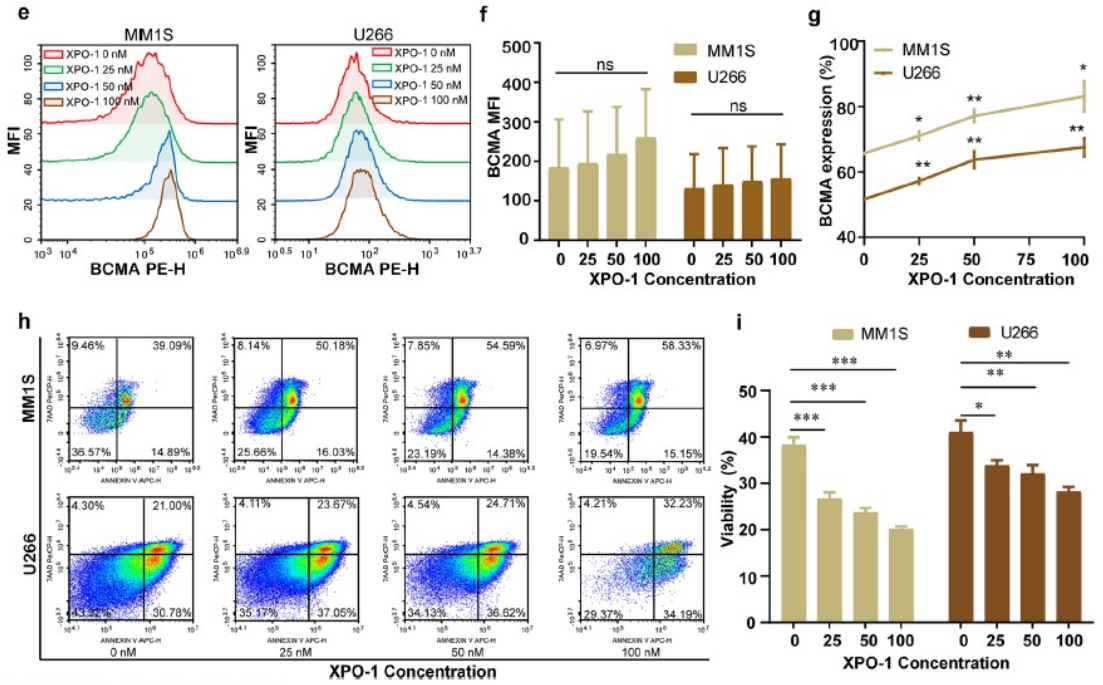
Dima D, et al. Abstract 897; oral presentation at ASH 2024.

XPO1 inhibition as a mechanism for enhancing BCMA-directed therapies

- Two cases of patients with R/R EMM treated with selinexor and BCMA CAR-T cell product CT103A
- A low dose of **selinexor** could **upregulate the expression of BCMA** on plasma cell lines and subsequently **enhance CAR-T cell function *in vitro***

The combination of selinexor and CT103A exerted a preliminary synergistic effect, and may be developed as a promising strategy for R/R EMM

Influence of selinexor on plasma cell and CAR T-cell *in vitro**



*e–g Flow cytometry was used to evaluate MFI and expression rate of BCMA on MM1S and U266 cell lines pre-treated with different concentrations of selinexor (0-100 nM). There was a slight but not statistically significant increase in MFI. Meanwhile, there was a significant increase of expression rate of surface BCMA with dose escalation. **h** Flow cytometry was used to assess the viability of different concentrations of selinexor (0-100 nM) pre-treated MM1S and U266 cell lines when co-cultured with CAR-T cells. **i** The statistical representation of diagram h. The cytotoxicity increased in a dose-dependent manner, which was statistically significant. *Statistically significant with $p < 0.05$, **$p < 0.01$, and ***$p < 0.0001$.

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMM, extramedullary multiple myeloma; MFI, mean fluorescence intensity; R/R, relapsed/refractory.

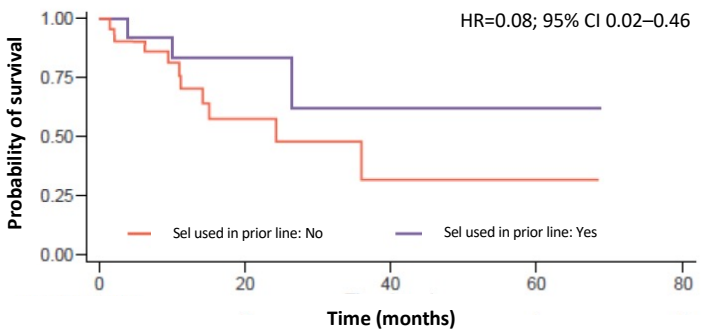
Wang D, et al. J Transl Med 2023;21:812.

Sequencing selinexor and BCMA-directed therapy

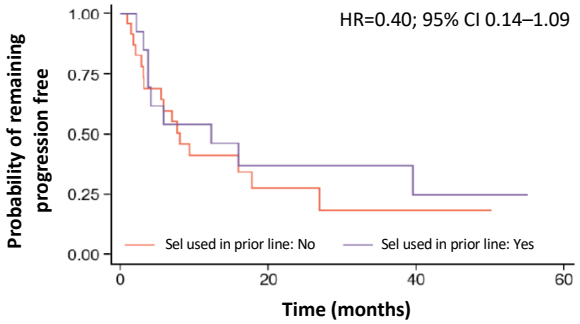
- In a retrospective cohort study, the impact of prior treatment with a selinexor-containing regimen on CAR-T outcomes was evaluated in patients with R/R MM
- The BCMA-directed CAR-T products administered included ide-cel (60%), cilta-cel (35.6%), and CC-98633/BMS-986354 (4.4%)

- At a median follow-up of 68 months, **median DoR was 8.1 months** (IQR 2.6–39), **median PFS was 8.1 months** (IQR 3.1–39.5), and **median OS was 35.9 months** (IQR 14.2–NR)

OS if selinexor was used in the immediate prior LOT before CAR-T therapy



PFS if selinexor was used in the immediate prior LOT before CAR-T therapy



Prior selinexor exposure did not compromise the efficacy or safety of anti-BCMA CAR-T in R/R MM, with **encouraging PFS and OS observed post-CAR-T in patients previously treated with selinexor**

Patients who received selinexor in the **therapy line immediately preceding CAR-T** demonstrated **longer PFS and OS** compared to those exposed in earlier lines

CAR, chimeric antigen receptor; CI, confidence interval; DoR, duration of response; HR, hazard ratio; IQR, interquartile range; LOT, line of therapy; MM, multiple myeloma; NR, not reached; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Costa BA, et al. J Clin Med 2025;14:1316.

Summary

There is a **lack of clear SoC** on the **use**, **combination** and **sequencing** of the growing number of **MM treatment options**, complicated by the heterogeneity of this population

Immunotherapies can cause detrimental effects on the immune system, potentially causing **T-cell exhaustion**

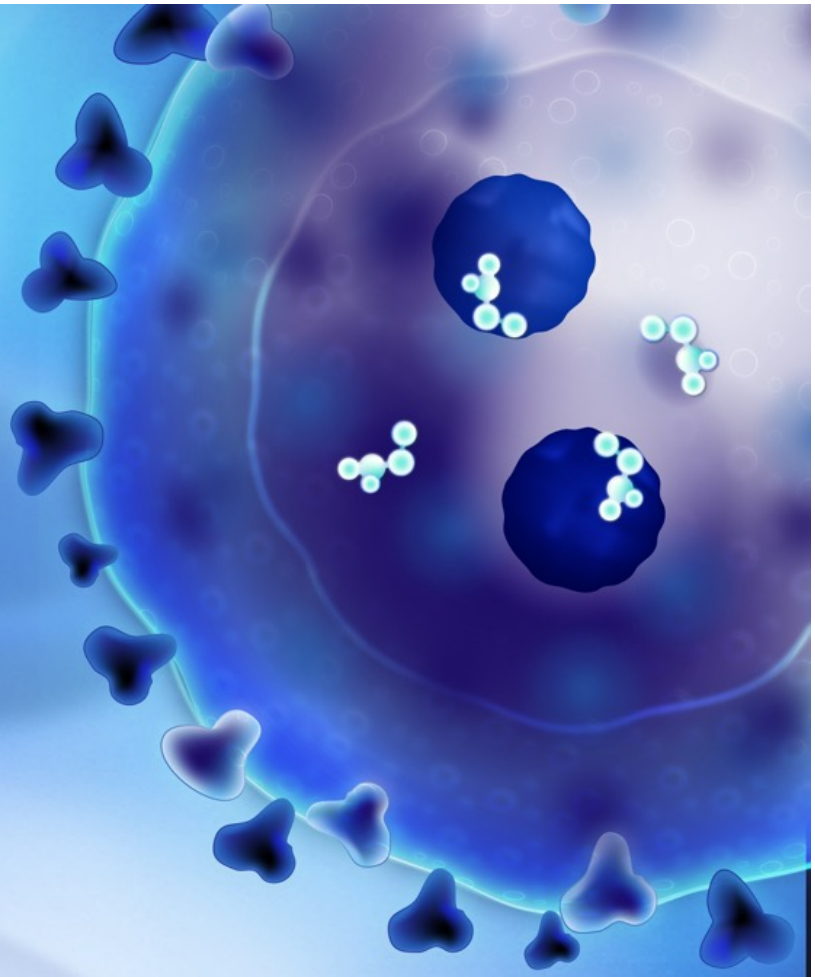
XPO1 inhibitors promote T-cell fitness and reduce T-cell exhaustion, and different studies have demonstrated the effect of selinexor on T-cell fitness

Incorporating **selinexor combinations as BCMA-free regimens** can enhance benefits and improve outcomes following **prior BCMA-directed therapy by optimising treatment sequencing**

BCMA, B-cell maturation antigen; MM, multiple myeloma; SoC, standard of care.

Q&A and closing remarks

Evangelos Terpos



MENARINI group

Stemline®
A Menarini Group Company

We value your feedback…

It’s time to complete your evaluation form!

Access via the QR code